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THE EUROPEAN PARLIAMENT **THE COUNCIL**

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DIRECTIVE
OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
ON THE UNION CODE RELATING TO MEDICINAL PRODUCTS FOR HUMAN USE, AND REPEALING DIRECTIVES 2001/83/EC AND 2009/35/EC

DIRECTIVE (EU) 2026/…
OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 25 November 2026

on the Union code relating to medicinal products for human use, and repealing Directives 2001/83/EC and 2009/35/EC

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Articles 114(1) and Article 168(4), point (c), thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Having regard to the opinion of the European Economic and Social Committee[1],

Having consulted the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure[2],

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1 OJ C, C/2024/879, 6.2.2024, ELI: http://data.europa.eu/eli/C/2024/879/oj.

2 Position of the European Parliament of 10 April 2024 (OJ C, C/2025/1328, 13.3.2025, ELI: http://data.europa.eu/eli/C/2025/1328/oj) and position of the Council at first reading of 28 September 2026 (OJ C, C/2026/5269, 16.10.2026, ELI: http://data.europa.eu/eli/C/2026/5269/oj). Position of the European Parliament of … (not yet published in the Official Journal).

Whereas:

(1) The Union general pharmaceutical legislation laid down in, inter alia, Directive 2001/83/EC of the European Parliament and of the Council[3], was established in 1965 with the dual objective of safeguarding public health and harmonising the internal market for medicinal products. It has developed considerably since then, but these overarching objectives have guided all revisions. The legislation governs the granting of marketing authorisations for all medicinal products for human use by defining conditions and procedures to enter and remain on the market. A fundamental principle is that a marketing authorisation is granted only to medicinal products with a favourable benefit-risk balance after assessment of their quality, safety and efficacy.

(2) The most recent comprehensive revision of the Union general pharmaceutical legislation took place between 2001 and 2004 while targeted revisions on post-authorisation monitoring (pharmacovigilance) and on falsified medicinal products were adopted subsequently. In the almost 20 years since the last comprehensive revision, the pharmaceutical sector has changed and has become more globalised, both in terms of development and manufacture. Moreover, science and technology have evolved at a rapid pace. However, there continues to be unmet medical needs, i.e. diseases without or only with suboptimal treatments for the concerned patient populations. Moreover, some patients might not benefit from innovation because medicinal products might be unaffordable or might not be placed on the market in the Member State concerned. There is also a greater awareness of the environmental impact of medicinal products. More recently, the COVID-19 pandemic has stress tested the legal framework.

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[3] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67, ELI: http://data.europa.eu/eli/dir/2001/83/oj).

(3) This Directive contributes to the implementation of the One Health Approach, stressing the well-established interconnectedness between human, animal and ecosystem health, and the need to include those three dimensions when addressing public health threats. Environmental stress and degradation, including biodiversity loss, contribute to the transmission of diseases between, and the disease burden on, humans and animals. In addition, pollution from active pharmaceutical ingredients negatively affects the quality of waters and ecosystems and causes antimicrobial resistance to increase rapidly, posing risks to public health globally.

(4) This Directive is part of the implementation of the 'Pharmaceutical strategy for Europe' adopted by the Commission in its communication of 25 November 2020. It aims to promote innovation, in particular for unmet medical needs, while reducing regulatory burden and the environmental impact of medicinal products; create an attractive environment for research, development and manufacturing of medicinal products in the Union; ensure access, including affordability, to innovative and established medicinal products for patients, with special attention to enhancing security of supply and addressing risks of shortages, taking into account the challenges of the smaller markets of the Union; and create a balanced and competitive system that ensures medicinal products remain affordable for health systems and patients while rewarding innovation.

(5) Complementarily to this Directive, the Union takes other actions, such as the 'Life Sciences Strategy' set out in the Commission communication of 2 July 2025, to strengthen the European pharmaceutical ecosystem to accelerate research and development of new medicinal products and support innovation.

(6) A range of Union programmes are used to fund pharmaceutical research projects, such as Horizon Europe, InvestEU, EU4Health, cohesion policy and the Digital Europe Programme. The Union is also to prioritise in its research agenda participation in cross-country collaboration enabling transnational research to meet public health needs.

(7) The essential aim of any rules governing the authorisation, manufacture, supervision, distribution and use of medicinal products is to safeguard public health. Such rules should also ensure the free movement of medicinal products and the elimination of obstacles to trade in medicinal products to all patients in the Union.

(8) This Directive is consistent with the Union's objectives with regard to promotion of research, innovation, digitalisation, trade, international development and industrial competitiveness.

(9) The legal framework for medicinal products for human use should also take into account the needs of the undertakings in the pharmaceutical sector and trade in medicinal products within the Union, without jeopardising the quality, safety and efficacy of medicinal products.

(10) As parties to the United Nations Convention on the Rights of Persons with Disabilities of 12 December 2006, the Union and its Member States are bound by its provisions to the extent of their competences. This includes the right to access information as set out in Article 21 of that Convention and the right to the enjoyment of the highest attainable standard of health without discrimination on the basis of disability as set out in Article 25 of that Convention.

(11) This Directive maintains the level of harmonisation that has already been achieved in Union pharmaceutical legislation. Where necessary and appropriate, it further reduces the remaining disparities, by laying down rules on the supervision and control of medicinal products and the rights and duties incumbent upon the competent authorities of the Member States with a view to ensuring compliance with legal requirements. In the light of experience gained from the application of the Union pharmaceutical legislation and the evaluation of its functioning, the legal framework needs to be adapted to scientific and technological progress, the current market conditions and economic reality within the Union. Scientific and technological developments induce innovation and development of medicinal products, including for therapeutic areas where there is still unmet medical need. To harness these developments, the Union pharmaceutical legislation should be adapted to meet scientific developments such as genomics, accommodate cutting-edge medicinal products, e.g. personalised medicinal products, novel treatments and technological transformation such as data analytics, digital tools and the use of artificial intelligence. These adaptations also contribute to the competitiveness of the Union pharmaceutical industry.

(12) The revision of Directive 2001/83/EC focuses on provisions that are relevant to achieve its specific objectives. It therefore covers all provisions except those concerning falsified medicinal products, homeopathic medicinal products and traditional herbal medicinal products. Nevertheless, for the sake of clarity, it is necessary to repeal Directive 2001/83/EC and replace it with a new Directive. The current provisions of Directive 2001/83/EC on falsified medicinal products, homeopathic medicinal products and traditional herbal medicinal products are therefore maintained in this Directive without substantive changes compared to previous harmonisations. However, in view of the changes in the governance of the European Medicines Agency (the 'Agency'), the Committee for Herbal Medicinal products is replaced by a working group. In addition, labelling requirements for homeopathic medicinal products have been updated to include additional information on the interaction between homeopathic medicinal products and other medicinal products.

(13) Without affecting the rules laid down in this Directive, Member States remain solely responsible for their own national security. They are responsible in defending their essential State functions, including ensuring their territorial integrity and safeguarding national security. In particular, under Article 346 of the Treaty on the Functioning of the European Union (TFEU), no Member State is obliged to supply information the disclosure of which it considers contrary to the essential interests of its security. For this reason, Member States should be able to waive some of the information requirements related to the marketing of medicinal products where those medicinal products are supplied for military or defence purposes and insofar as the application of such requirements implies a risk to national security or defence.

(14) Medicinal products for rare diseases and for children should be subject to the same conditions as any other medicinal product concerning their quality, safety and efficacy, for example as regards marketing authorisation procedures, quality and pharmacovigilance requirements. However, specific requirements also apply to them considering their unique characteristics. Such requirements, which are currently laid down in separate legal acts, should be integrated in the Union general pharmaceutical legal framework in order to ensure clarity and coherency of all the measures applicable to such medicinal products. Furthermore, as some medicinal products authorised for use in children are authorised by the Member States, specific provisions should be integrated in this Directive. It is important to address problems encountered which concern medicinal products for children, such as the failure to complete paediatric clinical studies or to obtain data required for marketing authorisation in a timely manner, which results in significant delay in the approval of medicinal products for children compared to approvals for medicinal products for adults.

(15) The system of a directive and regulation for the Union general pharmaceutical legislation should be maintained to avoid fragmentation of national legislation on medicinal products for human use, given that national legislation is based on a system of marketing authorisations granted by the competent authorities of the Member States (national marketing authorisations) and marketing authorisations granted by the Union (centralised marketing authorisations). National marketing authorisations are granted and managed on the basis of national law implementing the Union pharmaceutical legislation. The evaluation of the Union general pharmaceutical legislation has not shown that the choice of legal instrument has caused specific problems or created disharmonisation. In addition, REFIT Platform opinion, in the 2019 Annual Burden Survey, showed that there was no support among the Member States to turn Directive 2001/83/EC into a Regulation.

(16) This Directive should work in synergy with Regulation (EU) 2026/… of the European Parliament and of the Council[4+] to enable innovation and promote the competitiveness of the Union pharmaceutical industry, in particular of micro, small and medium-sized enterprises. In this respect, a balanced system of incentives is proposed that rewards innovation especially in areas of unmet medical need and innovation that stems from development in the Union. Moreover, companies are incentivised to apply early for marketing authorisations within the Union to bring innovation to the Union and its patients faster. To make the regulatory system more efficient and innovation-friendly, this Directive also aims to reduce administrative burden and simplify procedures for undertakings.

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4 Regulation (EU) 2026/… of the European Parliament and of the Council of … laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulations (EC) No 1394/2007 and (EU) No 536/2014 and repealing Regulations (EC) No 141/2000, (EC) No 726/2004 and (EC) No 1901/2006 (OJ L, …, ELI: …).

\+ OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)) and in the corresponding footnote the number, date of adoption and publication reference of that Regulation, including its ELI number.

(17) The definitions and the scope of Union pharmaceutical legislation should be clarified in order to achieve high standards for the quality, safety and efficacy of medicinal products and to address potential regulatory gaps, without changing the overall scope, due to scientific and technological developments, e.g. low-volume products, bedside-manufacturing or personalised medicinal products that do not involve an industrial manufacturing process.

(18) To avoid the duplication of requirements for medicinal products in this Directive and in Regulation (EU) 2026/…[+], the general standards in regard to quality, safety, efficacy and environmental risk of medicinal products laid down in this Directive should be applicable to medicinal products covered by a national marketing authorisation and also to medicinal products covered by a centralised marketing authorisation. Therefore, the requirements for a marketing authorisation application for a medicinal product should be valid for both, and the rules on prescription status, product information, regulatory data protection and regulatory market protection as well as the rules on manufacturing, supply, advertising, supervision and controls and other requirements should also be applicable to medicinal products covered by a centralised marketing authorisation.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(19) The determination of whether a product falls within the definition of a medicinal product is to be made on a case-by-case basis taking into account the factors set out in this Directive, such as the product's presentation or pharmacological, immunological or metabolic properties.

(20) In order to take account of both the emergence of new therapies and the growing number of so-called 'borderline' products between the medicinal product sector and other sectors, certain definitions and derogations should be modified, so as to avoid any doubt as to the applicable legislation. Similarly, it should be clarified that in situations where a product falls within the definition of a medicinal product under this Directive, but also falls within the definition of a product regulated under another legislative act, the rules for medicinal products under this Directive should apply. Furthermore, to ensure the clarity of applicable rules, it is also appropriate to improve the consistency of the terminology used in Union pharmaceutical legislation and clearly indicate the products excluded from the scope of this Directive.

(21) The new definition of a substance of human origin (SoHO) introduced by Regulation (EU) 2024/1938 of the European Parliament and the Council[5] covers any substance collected from the human body in whatever manner, whether it contains cells or not and regardless of whether it meets the definition of 'blood', 'tissue' or 'cell', for example human breast milk, intestinal microbiota and any other SoHO that may be applied to humans in the future. Such substances of human origin, other than tissues and cells, can become SoHO-derived medicinal products other than advanced therapy medicinal products (ATMPs), where the SoHO is subject to an industrial process involving pooling of donations, systematisation, reproducibility and operations performed on a routine basis or batch-wise resulting in a product of standardised consistency. The pooling of a limited number of donations for the preparation of SoHO is not in itself an industrial process. Where a process concerns extraction of an active ingredient from the SoHO, other than tissues and cells, or the transformation of a SoHO, other than tissues and cells, by changing its inherent properties, this should also be considered a SoHO-derived medicinal product. Where a process concerns concentrating, separating, inactivating pathogens or isolating elements, or a combination of those processes, in the preparation of SoHO, such a process in and of itself should normally not be considered as changing their inherent properties.

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[5] Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC (OJ L, 2024/1938, 17.07.2024, ELI: http://data.europa.eu/eli/reg/2024/1938/oj).

(22) According to current scientific knowledge, haptens, when combined with an endogenous carrier substance, are allergens and should be construed as such for the purpose of pharmaceutical legislation.

(23) For the avoidance of doubt, it is appropriate to underline that the safety and quality of human organs intended for transplantation are regulated exclusively by Directive 2010/53/EU of the European Parliament and of the Council[6], and the safety and quality of SoHO intended for medically assisted reproduction are regulated exclusively by Regulation (EU) 2024/1938.

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6 Directive 2010/53/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation (OJ L 207, 6.8.2010, p. 14, ELI: http://data.europa.eu/eli/dir/2010/53/oj).

(24) Advanced therapy medicinal products prepared within a Member State on a non-routine basis in accordance with specific quality standards and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product to meet the needs of an individual patient, should be subject to an exemption from the general requirements set out in this Directive and Regulation (EU) 2026/…[+], while ensuring that relevant Union rules relating to quality and safety are not undermined ('advanced therapy medicinal products prepared under hospital exemption'). Experience has shown that there are significant variations in the implementation of the hospital exemption among Member States. To improve the implementation of the hospital exemption, this Directive introduces measures for the collection and reporting of data as well as for the review of such data yearly by the competent authorities and their publication by the Agency in a repository. Furthermore, the Agency should prepare a report on the implementation of the hospital exemption based on contributions from Member States to assess whether an adapted framework should be developed for certain less complex ATMPs that have been developed and used under hospital exemption. If an approval for the manufacturing and use of an ATMP under hospital exemption is revoked due to safety concerns, the relevant competent authority of the Member State should notify the Agency, which should then disseminate that information to the other Member States' competent authorities.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(25) This Directive should be without prejudice to Council Directive 2013/59/Euratom[7], including with respect to justification and optimisation of the protection of patients and other individuals subject to medical exposure to ionising radiation. In the case of radiopharmaceuticals used for therapy, marketing authorisations, posology and administration rules are to comply with the requirements of that Directive as regards individual planning of exposures of target volumes, and the appropriate verification of their delivery, taking into account that doses to non-target volumes and tissues are to be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure.

[7] Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom (OJ L 13, 17.1.2014, p. 1, ELI: http://data.europa.eu/eli/dir/2013/59/oj).

(26) In the interest of public health, a medicinal product should only be allowed to be placed on the market in the Union if a marketing authorisation has been granted for that medicinal product, and if the quality, safety and efficacy of the medicinal product have been demonstrated. However, exemptions from those requirements should be provided for in situations characterised by an urgent need to administer a medicinal product to address the special needs of individual patients, or in the event of a suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation that could cause harm. In particular, in order to meet special needs, Member States should be allowed to exempt from the requirements set out in this Directive medicinal products supplied in response to a bona fide unsolicited order or anticipated bona fide unsolicited order, formulated or used in accordance with the specifications of an authorised healthcare professional and intended to meet the special needs of individual patients under the direct personal responsibility of that authorised healthcare professional. Member States should also be allowed to temporarily authorise the use and distribution of an unauthorised medicinal product in response to a suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.

(27) Pharmacies, including hospital pharmacies, play a crucial role in providing medicinal products to patients. They prepare specific medicinal products, known as magistral formulas, that are tailored to meet the special needs of individual patients based on the written instructions of a doctor. In certain situations, it is necessary, in order to cater for the needs of individual patients, to prepare those magistral formulas in advance on the basis of anticipated medical prescriptions within a specified period. This could include situations of urgency in which it is necessary for the magistral formula to be immediately available or situations where advance preparations are necessary to ensure dose accuracy or the quality of the medicinal product. Purely financial reasons should not justify the use of this possibility.

(28) Additionally, pharmacies are responsible for preparing standard medicinal products, referred to as officinal formulas. Those medicinal products are prepared in accordance with established guidelines found in pharmacopoeias. Officinal formulas are designed for general use and adhere to standardised recipes that are set by authoritative pharmaceutical bodies. Unlike magistral formulas, they are not customised for individual patients. Generally, those preparations should be exempt from the authorisation requirements set out in this Directive, but remain subject to national regulations.

(29) In exceptional cases, to ensure the availability of specific medicinal products or suitable alternatives for patients in a Member State, it should be possible for that Member State to exempt temporarily those medicinal products from the requirements set out in this Directive, to meet the specific needs of individual patients in that Member State. In addition, to mitigate shortages effectively in a Member State, it is important to address the patients' needs at population level and allow the preparation of such medicinal products, subject to strict conditions. Any other reasons, such as financial interests, should not be a justification for allowing those exemptions. Such exemptions should never aim to distort competition and should be interpreted narrowly, and only be used to mitigate or resolve a shortage in a Member State or in a situation where there is no relevant authorised medicinal product available on the market. Member States should, in any event, undertake their best efforts to find suitable alternatives under the rules set out in this Directive and in Regulation (EU) 2026/…[+].

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(30) It is recognised that improved access to information contributes to public awareness about the assessment and authorisation of medicinal products. When assessing the marketing authorisation application for a medicinal product, the competent authority of the Member State should draw up an assessment report on the quality, safety, efficacy, and the environmental risk assessment (ERA), as applicable, of the medicinal product and the reasons for its opinion. The competent authority of the Member State should make publicly available a summary of the assessment report and a summary of the ERA, after the deletion of any information of a commercially confidential nature and written in a manner that is understandable to the public. To the extent information under the ERA would entail environmental information within the meaning of Directive 2003/4/EC of the European Parliament and of the Council[8], the provisions of that Directive should apply.

(31) Marketing authorisation decisions should be taken on the basis of the objective scientific criteria of the quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic or any other considerations. However, Member States should be able exceptionally to prohibit the use in their territory of certain medicinal products.

(32) The particulars and documents that are to accompany a marketing authorisation application for a medicinal product should demonstrate that the therapeutic efficacy of the product overweighs potential risks. The benefit-risk balance of all medicinal products is assessed when they are placed on the market, and at any other time the competent authority of the Member State or the Agency, as applicable, deems appropriate.

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[8] Directive 2003/4/EC of the European Parliament and of the Council of 28 January 2003 on public access to environmental information and repealing Council Directive 90/313/EEC (OJ L 41, 14.2.2003, p. 26, ELI: http://data.europa.eu/eli/dir/2003/4/oj).

(33) In the context of the development and marketing authorisation of medicinal products, it is crucial that particular attention is given to the composition of clinical trials, to ensure comprehensive clinical data and, where appropriate, gender-based equity.

(34) As market forces alone have proven insufficient to stimulate adequate research into, and the development and marketing authorisation of, medicinal products for the paediatric population, a system of obligations, rewards and incentives should be established.

(35) It is therefore necessary to introduce a requirement for new medicinal products or when developing paediatric indications of already authorised products covered by a patent or a supplementary protection certificate to present either the results of studies in the paediatric population in accordance with an agreed paediatric investigation plan or proof of having obtained a waiver or deferral, at the time of filing a marketing authorisation application or an application for a new therapeutic indication, new pharmaceutical form or new route of administration. However, in order to avoid exposing patients, especially children, to unnecessary clinical trials or due to the nature of the medicinal products, that requirement should not apply to generic medicinal products or biosimilar medicinal products and medicinal products authorised through the well-established medicinal use procedure, nor should it apply to homeopathic medicinal products and traditional herbal medicinal products authorised through the simplified registration procedures set out in this Directive.

(36) In order to ensure that the data supporting the marketing authorisation concerning the paediatric use of a medicinal product to be authorised under this Directive and Regulation (EU) 2026/…[+] have been correctly developed, the competent authority of the Member State should check compliance with the agreed paediatric investigation plan and any waivers and deferrals during the scientific assessment of a valid marketing authorisation applications.

(37) For medicinal products covered by a supplementary protection certificate under Regulation (EC) No 469/2009 of the European Parliament and of the Council[9], a six month extension of that certificate should be granted by way of reward where all the measures included in the agreed paediatric investigation plan are complied with and relevant information on the results of the studies conducted is included in the product information.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

[9] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (OJ L 152, 16.6.2009, p. 1, ELI: http://data.europa.eu/eli/reg/2009/469/oj).

(38) Certain particulars and documents that are normally to be included in a marketing authorisation application should not be required if a medicinal product is a generic medicinal product or a biosimilar medicinal product that is authorised or has been authorised in the Union. Both generic medicinal products and biosimilar medicinal products are important to ensure access to medicinal products for a wider patient population, at more affordable prices, and create a competitive internal market. In a joint statement, the competent authorities of the Member States confirmed that the experience with approved biosimilar medicinal products over the past 15 years has shown that in terms of efficacy, safety and immunogenicity they are comparable to their reference medicinal product and are therefore interchangeable and can be used instead of their reference medicinal product (or vice versa) or replaced by another biosimilar medicinal product of the same reference medicinal product.

(39) Experience has shown that it is advisable to specify precisely the cases in which the results of toxicological and pharmacological tests or clinical studies do not have to be provided in order to obtain a marketing authorisation for a medicinal product that is essentially similar to an authorised medicinal product, while ensuring that innovative undertakings are not placed at a disadvantage. For such specified categories of medicinal products an abridged procedure should allow applicants to rely on data submitted by previous applicants and therefore to submit only some specific documentation.

(40) For generic medicinal products, only the equivalence of the generic medicinal product with the reference medicinal product should be demonstrated. For biosimilar medicinal products, only the results of comparability tests and studies should be provided to the competent authorities of the Member States or the Agency, as applicable. For hybrid medicinal products i.e. in cases where the medicinal product does not fall within the definition of a generic medicinal product or differs in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference medicinal product, the results of the relevant non-clinical tests or clinical studies should be provided to the extent necessary to establish a scientific bridge to the data relied upon in the marketing authorisation for the reference medicinal product. The same applies to bio-hybrid medicinal products i.e. in cases where the biological medicinal product does not fall within the definition of a biosimilar medicinal product or differs in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference biological medicinal product. Where applicable, a scientific bridge should establish that the active substance of the hybrid medicinal product or bio-hybrid medicinal product does not differ significantly in properties with regard to safety or efficacy. Where it differs significantly in respect of those properties, the marketing authorisation applicant should submit a full application.

(41) It should be possible for regulatory decision-making on the development, marketing authorisation and supervision of medicinal products to be supported by access to and analysis of health data, including real world data i.e. health data generated outside clinical studies, where appropriate. The competent authorities of the Member States or the Agency, as applicable, should be able to use such data, including via the European Health Data Space interoperable infrastructure. Data generated via *in silico* methods, such as computational modelling and simulation, molecular modelling, mechanistic modelling, digital twin and artificial intelligence, where appropriate, could also be used to support regulatory decision making.

(42) Any study involving the use of animals, which provides essential information on the quality, safety and efficacy of a medicinal product, should take into account the principles of replacement, reduction and refinement and apply them in accordance with Directive 2010/63/EU of the European Parliament and of the Council[10], where they concern the care and use of live animals for scientific purposes, and should only be used as necessary and be optimised in order to provide the most satisfactory results whilst using the minimum number of animals. The procedures of such testing should be designed to avoid causing pain, suffering, distress or lasting harm to animals and should follow the available guidelines of the Agency and of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The marketing authorisation applicant should not carry out animal tests where scientifically satisfactory non-animal testing methods are available. These can include: *in vitro* models, such as microphysiological systems including organs-on-chips, (2D and 3D) cell culture models, organoids and models based on human stem cells; *in silico* tools; *in chemico* technologies; and any combination thereof or read-across models. Where scientifically satisfactory non-animal testing methods are not available, applicants that use animal testing should ensure that the rules of Directive 2010/63/EU are applied, including the principles of reduction and refinement of animal testing for scientific purposes with regard to any animal study conducted for the purpose of supporting the application.

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[10] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (OJ L 276, 20.10.2010, p. 33, ELI: http://data.europa.eu/eli/dir/2010/63/oj).

(43) Procedures should be in place to facilitate joint animal testing, wherever possible, in order to avoid unnecessary testing using live animals in accordance with Directive 2010/63/EU. Marketing authorisation applicants and marketing authorisation holders should make all efforts to reuse animal study results and make the results obtained from animal studies publicly available. For abridged applications, marketing authorisation applicants should refer to the relevant studies conducted for the reference medicinal product.

(44) With respect to clinical trials, in particular those conducted outside the Union, on medicinal products destined to be authorised within the Union, it should be verified, at the time of the evaluation of the marketing authorisation application, that the trials were conducted in accordance with principles of good clinical practice and ethical requirements equivalent to those in Regulation (EU) No 536/2014 of the European Parliament and of the Council[11].

[11] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (OJ L 158, 27.5.2014, p. 1, ELI: http://data.europa.eu/eli/reg/2014/536/oj).

(45) There is the possibility, under certain circumstances, for marketing authorisations to be granted subject to specific obligations or conditions, on a conditional basis or under exceptional circumstances. This Directive should allow for medicinal products with a standard marketing authorisation for new therapeutic indications to be authorised on a conditional basis or under exceptional circumstances, under similar circumstances. The medicinal products authorised on a conditional basis or under exceptional circumstances should in principle satisfy the requirements for a standard marketing authorisation, with the exception of the specific derogations or conditions outlined in the relevant conditional or exceptional marketing authorisation, and should be subject to specific review of the fulfilment of the specific conditions or obligations imposed. The grounds for refusal of a marketing authorisation should apply *mutatis mutandis* to such cases.

(46) In justified cases, even when comprehensive safety and efficacy data have been supplied, post-authorisation studies could be imposed by the competent authorities of the Member States to enhance the safe and effective use of the medicinal product or to allow for evidence-based treatment optimisation.

(47) Furthermore, it should be possible to impose on marketing authorisation holders an obligation to conduct post-authorisation ERA studies, to collect monitoring data or information on use, or to implement appropriate risk mitigation measures, where identified or potential concerns about risks to the environment or public health, including antimicrobial resistance, need to be further investigated or mitigated after the medicinal product has been marketed.

(48) Where the competent authorities consider that there are reasons to believe that a medicinal product could present a potential serious risk to public health, a scientific evaluation of the medicinal product should be undertaken, subject to the relevant procedures, leading to a decision to maintain, vary, suspend or revoke the marketing authorisation. The competent authorities should also be able to act where the conditions attached to the authorisation are not complied with, including the obligation to conduct post-authorisation ERA studies.

(49) With the exception of those medicinal products that are subject to the centralised marketing authorisation procedure established by Regulation (EU) 2026/…[+], a marketing authorisation for a medicinal product should be granted by a competent authority in one Member State. In order to avoid unnecessary administrative and financial burdens for marketing authorisation applicants and the competent authorities of the Member States, a full in-depth assessment of a marketing authorisation application for a medicinal product should be carried out only once. It is appropriate therefore to lay down special procedures for the mutual recognition of national marketing authorisations. Moreover, it should be possible to submit the same marketing authorisation application through the decentralised procedure in parallel in several Member States for the purpose of a common assessment under the lead of one of the Member States concerned.

(50) Moreover, rules should be established under those authorisation procedures to resolve any disagreements between Member States in a coordination group for decentralised and mutual recognition procedures (the 'coordination group') relating to medicinal products without undue delay. In the event of a disagreement between Member States about the quality, the safety or the efficacy of a medicinal product, a scientific assessment of the matter should be undertaken according to a Union standard, leading to a single decision on the points of disagreement, which should be binding on the Member States concerned. That decision should be adopted following a rapid procedure ensuring close cooperation between the Commission and the Member States.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(51) In cases of major disagreement that cannot be solved, the case should be settled by means of a Commission Decision. However, it should be possible to refer the matter to the Committee for Medicinal Products for Human Use for a scientific opinion before the Commission adopts its decision by means of an implementing act.

(52) In order to better protect public health and avoid any unnecessary duplication of effort during the examination of marketing authorisation applications for medicinal products, Member States should systematically draw up an assessment report in respect of each medicinal product that is authorised by them, and exchange reports upon request. Furthermore, a Member State should be able to suspend the examination of a marketing authorisation application for a medicinal product that is under active consideration in another Member State with a view to recognising the decision reached by the latter Member State.

(53) In order to ensure as broad as possible access to medicinal products, a Member State that is interested in having access to a particular medicinal product for which a marketing authorisation is applied for under the decentralised or mutual recognition procedure should be able to opt into the procedure and become a Member State concerned by that procedure.

(54) In order to increase availability of medicinal products, in particular on smaller markets, in cases where an applicant does not apply for a marketing authorisation for a medicinal product in the context of the mutual recognition procedure in a given Member State, it should be possible for that Member State to authorise the placing on the market of the medicinal product where justified for public health reasons.

(55) In the case of generic medicinal products for which the reference medicinal product has been granted a marketing authorisation under the centralised procedure, applicants seeking a marketing authorisation should be able to choose either of the two procedures, namely the national procedure or the centralised procedure, on certain conditions. Similarly, the decentralised or mutual recognition procedure should remain available as an option for certain medicinal products, even if they represent a therapeutic innovation or are of benefit to society or to patients. Since generic medicinal products account for a major part of the market in medicinal products, their access to the Union market should be facilitated in the light of the experience acquired and the procedures to involve other Member States concerned in the marketing authorisation procedure should be therefore further simplified.

(56) The simplification of procedures should not have an impact on standards or the quality of scientific evaluation of medicinal products to guarantee the quality, safety and efficacy of medicinal products and therefore, the scientific evaluation period should, in principle, remain the same. However, this Directive provides for the reduction of the overall period for marketing authorisation procedure from 210 days to 180 days.

(57) Member States should ensure that adequate financial resources are available to the competent authorities of the Member States in order for them to carry out their tasks under this Directive and Regulation (EU) 2026/…[+]. In addition, Member States should ensure that adequate resources are assigned by the competent authorities of the Member States for the purpose of their contributions to the work of the Agency, taking into account the cost-based remuneration they receive from the Agency.

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(58) As regards access to medicinal products, previous amendments to the Union pharmaceutical legislation have addressed this issue by providing for accelerated assessment of marketing authorisation applications or by allowing conditional marketing authorisations for medicinal products which address unmet medical needs. While those measures accelerated the authorisation of innovative and promising therapies in some areas, certain public health priorities remain unaddressed. Additionally, those medicinal products do not always reach the patient and patients in the Union still have different levels of access to medicinal products. Patient access to medicinal products depends on many factors. Marketing authorisation holders are not obliged to market a medicinal product in all Member States; they can decide not to market their medicinal products in, or withdraw them from, one or more Member States, often due to commercial reasons. National pricing and reimbursement policies, the size of the population, the organisation of health systems and national administrative procedures are other factors influencing market launch and patient access.

(59) Addressing unequal patient access and affordability of medicinal products have become key priorities of the Pharmaceutical Strategy for Europe, as also highlighted by Council conclusions of 17 June 2016 on strengthening the balance in the pharmaceutical systems in the European Union and its Member State[12] and of 15 June 2021 on access to medicines and medical devices for a stronger and resilient EU[13] and the European Parliament resolution of 2 March 2017 on EU options for improving access to medicines[14]. Member States called for revised mechanisms and incentives for the development of medicinal products, tailored to the level of unmet medical needs, while ensuring health system sustainability, patient access and availability of affordable medicinal products in all Member States. Monitoring and evaluating access to medicinal products at Union level is important to understand the results achieved.

(60) Access to medicinal products also comprises affordability. In this regard, the Union pharmaceutical legislation respects the competence of the Member States in terms of pricing and reimbursement. In a complementary manner, it aims to have a positive impact on affordability and sustainability of health systems with measures that support competition from generic medicinal products and biosimilar medicinal products. The competition from generic medicinal products and biosimilar medicinal products should also, in turn, improve patients' access to medicinal products.

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12 OJ C 269, 23.7.2016, p. 31.
13 OJ C 269I, 7.7.2021, p. 3.
14 OJ C 263, 25.7.2018, p. 4.

(61) To ensure dialogue among all actors in the medicinal products lifecycle, discussions on policy issues related to the application of the rules related to access to and availability of medicinal products should take place in the Pharmaceutical Committee. It should be possible for the Commission to invite bodies responsible for health technology assessment as referred to in Regulation (EU) 2021/2282 of the European Parliament and of the Council[15] or national bodies responsible for pricing and reimbursement, as required, to participate in the deliberations of the Pharmaceutical Committee.

(62) While pricing and reimbursement decisions are a Member State competence, the Pharmaceutical Strategy for Europe announced actions to support cooperation of Member States to improve affordability. The Commission has transformed the group of National Competent Authorities on Pricing and Reimbursement and public healthcare payers (NCAPR) from an ad hoc forum to a continuous voluntary cooperation with the aim to exchange information and best practices on pricing, payment and procurement policies to improve the affordability and cost-effectiveness of medicinal products and health system's sustainability. The Commission is committed to stepping up this cooperation and further supporting information exchange among national authorities, including on public procurement of medicinal products, while fully respecting the competences of Member States in this area. It should also be possible for the Commission to invite NCAPR members to participate in deliberations of the Pharmaceutical Committee on topics that may have an impact on pricing or reimbursement policies, such as the market launch incentives provided for in this Directive.

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15 Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (OJ L 458, 22.12.2021, p. 1, ELI: http://data.europa.eu/eli/reg/2021/2282/oj).

(63) Joint procurement, whether within a country or across countries, can improve access to as well as affordability and security of supply of medicinal products, in particular for smaller countries. Member States interested in joint procurement of medicinal products can make use of Directive 2014/24/EU of the European Parliament and of the Council[16], which sets out purchasing procedures for public buyers, and Regulations (EU) 2022/2371[17] and (EU, Euratom) 2024/2509[18]of the European Parliament and of the Council. Upon request from the Member States, the Commission can support interested Member States by facilitating coordination to enable access to medicinal products for patients in the Union as well as information exchange, in particular for medicinal products for rare and chronic diseases.

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16 Directive 2014/24/EU of the European Parliament and of the Council of 26 February 2014 on public procurement and repealing Directive 2004/18/EC (OJ L 94, 28.3.2014, p. 65, ELI: http://data.europa.eu/eli/dir/2014/24/oj).

17 Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU (OJ L 314, 6.12.2022, p. 26, ELI: http://data.europa.eu/eli/reg/2022/2371/oj).

18 Regulation (EU, Euratom) 2024/2509 of the European Parliament and of the Council of 23 September 2024 on the financial rules applicable to the general budget of the Union (OJ L, 2024/2509, 26.9.2024, ELI: http://data.europa.eu/eli/reg/2024/2509/oj).

(64) The establishment of a criteria-based definition of 'unmet medical need' is necessary to incentivise the development of medicinal products in therapeutic areas that are currently underserved. To ensure that the concept of unmet medical need reflects scientific and technological developments and current knowledge in underserved diseases, the Agency should, in the form of scientific guidelines, specify the conditions concerning clinically relevant improvement in efficacy, or in safety with at least comparable efficacy, in comparison with existing medicinal products or other methods of prevention, diagnosis or treatment authorised in the Union. The guidelines should cover clinical efficacy endpoints such as survival, symptoms and health-related quality of life, and clinical safety endpoints such as side effects, and provide further technical details regarding their assessment. The Agency should seek input from a broad range of authorities or bodies active along the lifecycle of medicinal products in the framework of the consultation process established under Regulation (EU) 2026/…[+] and also take into account scientific initiatives at Union level or between Member States related to analysing unmet medical needs, burden of disease and priority setting for research and development. The Agency should also seek input from other relevant stakeholders, including relevant patient populations.

(65) The inclusion of new therapeutic indications in an authorised medicinal product contributes to improving patients' access to additional therapies and therefore should be incentivised.

(66) Repurposing of medicinal products to new therapeutic indications should be supported as it can provide significant health benefits to patients in a timely and affordable manner.

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(67) For marketing authorisation applications for medicinal products containing a new active substance, the submission of clinical trials that include an evidence-based existing treatment as a comparator, in line with scientific advice provided by the Agency, should be incentivised. This is in order to foster the generation of comparative clinical evidence that is relevant and that can therefore be used to support subsequent health technology assessments and decisions on pricing and reimbursement by Member States.

(68) The competent authorities of the Member States and the Agency should support the design of comparative clinical trials, wherever possible, when providing pre-authorisation scientific advice.

(69) The holder of a marketing authorisation for a medicinal product placed on the market in a Member State should, within the limits of its responsibility, ensure the appropriate and continuous supply of a medicinal product throughout its lifetime, including by maintaining appropriate stock levels, to wholesale distributors, pharmacies or other persons authorised to supply medicinal products so that the needs of patients in the Member State in question are met. Member States may specify in their national legislation the obligation for the marketing authorisation holder to ensure adequate supply of medicinal products to wholesale distributors in order to guarantee that the needs of patients in the Member States concerned are met.

(70) Access to medicinal products in all Member States and guaranteeing a timely, stable, reliable and high-quality supply of medicinal products are essential objectives to achieve an overall high level of protection of human health in the Member States, thus contributing to the protection of human health and human life in the Union. The responsibility of ensuring a timely, adequate and continuous supply of medicinal products so that the needs of patients in a Member State are covered rests, mainly, on the marketing authorisation holder. In principle, when a marketing authorisation is granted, the medicinal product is placed on the market by the marketing authorisation holder on its own initiative. Practice shows, however, that in certain Member States the placing on the market of authorised medicinal products does not occur or is delayed or occurs in quantities that do not correspond to the needs of those Member States. Therefore, Member States should, based on grounds of public health protection with due regard to the principle of proportionality and in compliance with Union law, in particular concerning the free movement of goods and competition, be able to require from the marketing authorisation holder specific actions with a view to complying with its market launch and supply obligations under this Directive and Regulation (EU) 2026/…[+]. To this aim, Member States should be able to request the marketing authorisation holder to do one or more of the following actions: to submit a valid pricing and reimbursement application, to participate in any relevant national or Union procurement procedures or to establish and implement a roll-out plan that is acceptable for the Member State concerned. The implementation of the roll-out plan should ensure sufficient and continuous supply to meet the needs of the patients in the Member State concerned.

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(71) A roll-out plan aims to ensure a predictable and continuous supply of medicinal products in a given Member State. It responds to the need of coordinated planning between the marketing authorisation holder and the competent authorities of the Member States. It would allow national authorities to anticipate availability and plan public-health measures and companies to plan manufacturing and distribution. Following a request by a Member State, the marketing authorisation holder should prepare a draft roll-out plan specifying the quantities and timing of supply of the medicinal product for a defined period of time taking into account the supply needs declared by the Member State and other objective considerations such as manufacturing or distribution capacity. Based on the draft roll-out plan submitted by the marketing authorisation holder, the Member State concerned and the marketing authorisation holder should discuss the plan, which will require the final agreement of the Member State concerned. Later, both the Member State and the marketing authorisation holder may require an update of the roll-out plan, to reflect any important developments such as evolving demand, or changes in manufacturing or distribution capacity. For the development, agreement, adaptation and effective implementation of the roll-out plan, the marketing authorisation holder and the Member State should be obliged to cooperate fully and provide timely and accurate information.

(72) Marketing authorisation holders and Member States should do their utmost to achieve a mutually agreed supply of medicinal products in accordance with the needs of the Member State concerned, without unduly delaying the other party’s exercise of its rights under this Directive or unduly impeding the exercise of those rights.

(73) Cross-border healthcare, including under Directive 2011/24/EU, is an additional pathway for patients to access a treatment that might otherwise not be available to them, notably in cases where the medicinal product cannot be administered to the patient in their home Member State.

(74) The possibility of using compulsory licences in situations of national emergency or other circumstances of extreme urgency is explicitly provided for under the Agreement on Trade-Related Aspects of Intellectual Property Rights (the 'TRIPS Agreement')[19]. Where a compulsory licence has been granted by a relevant authority in the Union pursuant to Regulation (EU) 2025/2645 of the European Parliament and of the Council[20] or under national compulsory licensing frameworks, regulatory data protection or regulatory market protection can, if still in force, prevent the effective use of the compulsory licence as it impedes the authorisation of generic medicinal products, and thus access to the medicinal products needed to address a crisis. For this reason, regulatory data protection and regulatory market protection should be suspended when a compulsory licence has been issued. Such a suspension of the regulatory data protection and regulatory market protection should be allowed only in relation to the compulsory licence granted and its beneficiary. The suspension should comply with the objective, the territorial scope, the duration and the subject matter of the granted compulsory licence.

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19 OJ L 336, 23.12.1994, p. 214.

20 Regulation (EU) 2025/2645 of the European Parliament and of the Council of 16 December 2025 on compulsory licensing for crisis management and amending Regulation (EC) No 816/2006 (OJ L, 2025/2645, 30.12.2025, ELI: http://data.europa.eu/eli/reg/2025/2645/oj).

(75) The suspension of the regulatory data protection and of the regulatory market protection should be granted only for the duration of the compulsory licence in the Member States where the compulsory licence has been granted. A suspension of the regulatory data protection and the regulatory market protection means that the regulatory data protection and the regulatory market protection produce no effect in relation to the particular licensee of the compulsory licence while that compulsory licence is in effect. When the compulsory licence ends, the regulatory data protection and the regulatory market protection should resume. However, the period of compulsory licensing should not be recouped, and therefore the suspension should not result in an extension of the original duration of the regulatory protection.

(76) It is currently possible for applicants for marketing authorisation for generic, biosimilar, hybrid and bio-hybrid medicinal products to conduct studies, trials and activities to fulfil the subsequent practical requirements necessary to obtain regulatory approvals for those medicinal products during the term of protection of the patent or supplementary protection certificate of the reference medicinal product, without this being considered as a patent or supplementary protection certificate infringement. The application of this limited exception is, however, fragmented across the Union and it is considered necessary, in order to facilitate the market entry of generic, biosimilar, hybrid and bio-hybrid medicinal products, to clarify the scope of this exception in order to ensure a harmonised application thereof in all Member States, both in terms of beneficiaries and in terms of the activities covered. The exception must be limited to conducting the necessary studies, trials and other activities needed to obtain a marketing authorisation, conduct health technology assessments and obtain pricing and reimbursement approvals as well as submit an application for procurement tenders, to the extent that the submission of an application for procurement tenders does not entail the sale or offering for sale of the medicinal product concerned during the term of protection, even though those activities can require substantial amounts of test production to demonstrate reliable manufacturing. During the term of protection of the patent or supplementary protection certificate of the reference medicinal product, there can be no commercial use of the final medicinal products obtained for the purposes of the regulatory approval process.

(77) The exception should allow inter alia, to conduct studies to support pricing and reimbursement approvals as well as the manufacture or purchase of patent protected active substances for the purpose of seeking marketing authorisations during the term of protection of the patent or supplementary protection certificate of the reference medicinal product, contributing to the market entry of generic and biosimilar medicinal products the first day following the expiry of the term of protection of the patent or supplementary protection certificate, and timely access to these products.

(78) The competent authorities should refuse to validate a marketing authorisation application referring to data of a reference medicinal product only on the basis of the grounds set out in this Directive. The same applies to any decision to grant, vary, suspend, restrict or revoke a marketing authorisation. The competent authorities cannot base their decision on any other grounds. In particular, such decisions should not be based on the patent or supplementary protection certificate status of the reference medicinal product. It also stems from those rules that the protection of intellectual property rights is not a valid ground to refuse, revoke or suspend decisions related to relevant pricing and reimbursement approvals, health technology assessment procedures, or where applicable, applications for procurement tenders. Member States remain free to introduce rules to ensure the readiness to supply a medicinal product on their market for the period following the expiry of the term of protection of the patent or supplementary protection certificate.

(79) The One Health Approach is needed in order to address antimicrobial resistance, one of the most significant, current health threats. High levels of cooperation are required across sectors and globally. This Directive puts in place coordinated action in order to ensure prevention and minimisation of environmental risks throughout the supply chain and use and disposal of antimicrobials, to raise awareness among patients, consumers and healthcare professionals and to promote the prudent and responsible use of antimicrobials.

(80) In order to address the challenge of antimicrobial resistance, where a pack of antimicrobials is intended for direct dispensing to patient, antimicrobials should be packaged in quantities that are appropriate for the therapy cycle relevant for that medicinal product and national rules on antimicrobials subject to medical prescription should ensure that those are dispensed in a way that corresponds to the quantities described by the medical prescription.

(81) The provision of information to healthcare professionals and to patients on the appropriate use, storage and disposal of antimicrobials is the joint responsibility of marketing authorisation holders and of Member States. Member States should ensure that an appropriate collection and management system is in place for all unused or expired medicinal products.

(82) Pharmacists and other healthcare professionals should play a role in antimicrobial stewardship, including advising on the prudent use of antibiotics and other antimicrobials, as well as on their correct disposal.

(83) While this Directive restricts the use of antimicrobials by setting categories of antimicrobials that are subject to medical prescription, due to the growing antimicrobial resistance in the Union, the competent authorities of the Member States should consider further measures such as expanding the prescription status of antimicrobials, initiatives for prudent use of antimicrobials in hospitals taking into account that the combined use of several antimicrobial active substances may represent a particular risk, sufficient training of healthcare professionals on stewardship regarding the use of antimicrobials and the mandatory use of diagnostic tests before prescription. The competent authorities of the Member States should consider such further measures according to the level of antimicrobial resistance in their territory and the needs of patients. With regards to antimicrobials for topical use, Member States should have the possibility to waive the mandatory ‘subject to medical prescription’ status, including taking into account the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form and certain types of packaging.

(84) The pollution of waters and soils with pharmaceutical residues is an emerging environmental problem, and there is scientific evidence that the presence of those substances in the environment resulting from their manufacture, use and disposal poses a risk to the environment and public health. The evaluation of the legislation showed that strengthening of existing measures to reduce the impact of medicinal products' lifecycle on the environment and public health is required. Measures under this Directive complement the main environmental legislation, in particular Council Directive 91/271/EEC[21] as well as Directives 2000/60/EC[22], 2006/118/EC[23], 2008/98/EC[24], 2008/105/EC[25], 2010/75/EU[26] and (EU) 2020/2184[27] of the European Parliament and of the Council.

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21 Council Directive 91/271/EEC of 21 May 1991 concerning urban waste water treatment (OJ L 135, 30.5.1991, p. 40, ELI: http://data.europa.eu/eli/dir/1991/271/oj).

22 Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy (OJ L 327, 22.12.2000, p. 1, ELI: http://data.europa.eu/eli/dir/2000/60/oj).

23 Directive 2006/118/EC of the European Parliament and of the Council of 12 December 2006 on the protection of groundwater against pollution and deterioration (OJ L 372, 27.12.2006, p. 19, ELI: http://data.europa.eu/eli/dir/2006/118/oj).

24 Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste and repealing certain Directives (OJ L 312, 22.11.2008, p. 3, ELI: http://data.europa.eu/eli/dir/2008/98/oj).

25 Directive 2008/105/EC of the European Parliament and of the Council of 16 December 2008 on environmental quality standards in the field of water policy, amending and subsequently repealing Council Directives 82/176/EEC, 83/513/EEC, 84/156/EEC, 84/491/EEC, 86/280/EEC and amending Directive 2000/60/EC of the European Parliament and of the Council (OJ L 348, 24.12.2008, p. 84, ELI: http://data.europa.eu/eli/dir/2008/105/oj).

26 Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial and livestock rearing emissions (integrated pollution prevention and control) (OJ L 334, 17.12.2010, p. 17, ELI: http://data.europa.eu/eli/dir/2010/75/oj).

27 Directive (EU) 2020/2184 of the European Parliament and of the Council of 16 December 2020 on the quality of water intended for human consumption (OJ L 435, 23.12.2020, p. 1, ELI: http://data.europa.eu/eli/dir/2020/2184/oj).

(85) Marketing authorisation applications for medicinal products in the Union should include an ERA and risk mitigation measures. However, when preparing their ERAs, the applicants for marketing authorisations of generic medicinal products and biosimilar medicinal products should be able to refer to ERA studies conducted for the reference medicinal product or to ERA studies conducted for any other medicinal product containing the same active substances. The same applies to hybrid medicinal products and bio-hybrid medicinal products as well as to fixed-dose combination medicinal products. If applicants fail to submit a complete or sufficiently substantiated ERA or if they do not propose risk mitigation measures to sufficiently address the risks identified in the ERA, the marketing authorisation should be refused. The ERA should be updated when new data or knowledge about relevant risks become available.

(86) Marketing authorisation applicants should take into account risk assessment procedures under other Union legal frameworks that may apply to chemicals depending on their use. In addition to this Directive, there are four main other legal frameworks: (i) Regulation (EC) No 1907/2006 of the European Parliament and of the Council[28] (industrial chemicals (REACH)); (ii) Regulation (EU) No 528/2012 of the European Parliament and of the Council[29] (biocides); (iii) Regulation (EC) No 1107/2009 of the European Parliament and of the Council[30] (pesticides); and (iv) Regulation (EU) 2019/6 of the European Parliament and of the Council[31] (veterinary medicinal products). In its communication on the European Green Deal of 11 December 2019, the Commission proposed a 'one-substance one-assessment' (OS-OA) approach for chemicals, in order to increase the efficiency of the registration system, reduce costs and unnecessary animal testing.

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28 Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (OJ L 396, 30.12.2006, p. 1, ELI: http://data.europa.eu/eli/reg/2006/1907/oj).

29 Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products (OJ L 167, 27.6.2012, p. 1, ELI: http://data.europa.eu/eli/reg/2012/528/oj).

30 Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC (OJ L 309, 24.11.2009, p. 1, ELI: http://data.europa.eu/eli/reg/2009/1107/oj).

31 Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (OJ L 4, 7.1.2019, p. 43, ELI: http://data.europa.eu/eli/reg/2019/6/oj).

(87) The emissions and discharges of antimicrobials to the environment from manufacturing sites can lead to antimicrobial resistance, which is a global concern regardless where the emissions and discharges take place. Therefore, the scope of the ERA should be extended to cover the risk of antimicrobial resistance selection throughout the entire life cycle of antimicrobials, including manufacturing. In order to specify technical details to conduct the ERA, the Agency should issue guidelines on how to measure antimicrobial resistance other than antibiotic resistance.

(88) This Directive should also include provisions for a risk-based approach regarding the ERA obligations of marketing authorisation holders before October 2005 and the setting-up of an ERA monograph system for active substances. This ERA monograph system should be available to applicants for use when conducting an ERA for a new marketing authorisation application.

(89) For medicinal products authorised prior to October 2005, which have not been the subject of an ERA, specific provisions should be introduced to set up a risk-based prioritisation programme for the ERA submission or update by the marketing authorisation holders. For generic, biosimilar, hybrid and bio-hybrid medicinal products and fixed-dose combination medicinal products, for which the reference medicinal product was authorised before 30 October 2005 and is included in that programme, the ERA could be submitted after the outcome of the ERA for the relevant reference medicinal product has been made publicly available by the Agency, unless the marketing authorisation holders concerned have participated in a joint ERA study conducted for the relevant active substance. The same should apply for new marketing authorisation applications for such generic, biosimilar, hybrid and bio-hybrid medicinal products and fixed-dose combination medicinal products for which the reference medicinal product was authorised before 30 October 2005 and is included in that programme.

(90) Northern Ireland has historically relied on the supply of medicinal products from or through parts of the United Kingdom other than Northern Ireland. Following the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community, to prevent shortages of medicinal products and ultimately to ensure a high level of public health protection, specific provisions have been put in place. This Directive replaces Directive 2001/83/EC listed in point 20 of Annex 2 to the Protocol on Ireland / Northern Ireland (the 'Windsor Framework') and would therefore apply to and in the United Kingdom in respect of Northern Ireland in accordance with Article 5(4) of the Windsor Framework, read in conjunction with Article 13(3) thereof. To ensure the continued effectiveness of the specific provisions that have already been put in place, it is therefore appropriate to stipulate that certain provisions of this Directive should not apply to and in the United Kingdom in respect of Northern Ireland. The power to adopt acts in accordance with Article 290 TFEU should be delegated to the Commission in order to amend or supplement certain rules whose application is to be suspended where the Commission finds that the level of protection of public health ensured by the United Kingdom is no longer essentially equivalent to that guaranteed within the Union or where sufficient information is not available to the Commission to enable it to establish whether an essentially equivalent level of protection of public health is ensured by the United Kingdom and that situation is not remedied within the specified time limit. It is of particular importance that the Commission carry out appropriate consultations during its preparatory work, including at expert level, and that those consultations be conducted in accordance with the principles laid down in the Interinstitutional Agreement of 13 April 2016 on Better Law-Making[32]. In particular, to ensure equal participation in the preparation of delegated acts, the European Parliament and the Council receive all documents at the same time as Member States' experts, and their experts systematically have access to meetings of Commission expert groups dealing with the preparation of delegated acts.

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[32] OJ L 123, 12.5.2016, p. 1, ELI: http://data.europa.eu/eli/agree_interinstit/2016/512/oj.

(91) To ensure that all children in the Union have access to medicinal products specifically authorised for paediatric use, when an agreed paediatric investigation plan has led to the authorisation of a paediatric indication for a medicinal product already marketed for other therapeutic indications, the marketing authorisation holder should be obliged to place the medicinal product on the same markets within two years of the date on which the medicinal product is authorised for that paediatric indication.

(92) It is necessary in the interest of public health to ensure the continuing availability of safe and effective medicinal products authorised for paediatric indications. Therefore, if a marketing authorisation holder intends to withdraw such a medicinal product from the market, arrangements should be in place so that the paediatric population can continue to have access to the medicinal product in question. In order to help achieve this, the competent authorities of the Member States or the Agency, as applicable, should be informed in good time of any such intention and should make that intention publicly available.

(93) To avoid unnecessary administrative and financial burdens both for the marketing authorisation holders and the competent authorities of the Member States or the Agency, as applicable, certain streamlining measures should be introduced, in line with the digital by default principle. Electronic applications for marketing authorisations and for variations of the terms of marketing authorisations should be introduced.

(94) As a general rule, risk management plans should not be developed or submitted for generic medicinal products and biosimilar medicinal products, considering that the reference medicinal product has such a plan, except in specific cases where a risk management plan should be provided. In addition, risk management plans for hybrid medicinal products and bio-hybrid medicinal products should be limited to the differences between those medicinal products and the reference medicinal product, as indicated in the marketing authorisation application, provided that no additional risk minimisation measures exist for the reference medicinal product and that the marketing authorisation for the reference medicinal product has not been withdrawn prior to the submission of the application.

(95) As a general rule, marketing authorisations should be granted for an unlimited period. Where, by way of derogation, a national marketing authorisation has been granted for a limited period, it should be possible for the marketing authorisation holder to submit an application for a renewal of that authorisation. Decisions on renewals should be based only on a re-evaluation of the benefit-risk balance of the medicinal product.

(96) In the event of a risk to public health, the marketing authorisation holder or the competent authorities of the Member States or the Commission should be able to impose urgent safety or efficacy restrictions on their own initiative. In such cases, when the Union interest referral procedure is launched, any duplication of assessments should be avoided.

(97) To address patients' needs, an increasing number of innovative medicinal products derive from or are combined with other medicinal products that may be manufactured or tested and regulated under more than one Union legal framework. Similarly, the same sites are increasingly overseen by authorities established under different Union legal frameworks. To ensure safe and efficient production and supervision of such products and appropriate delivery to patients, it is important to ensure consistency between those frameworks. Consistency and proper alignment can only be ensured through appropriate cooperation in the development of the practices and principles applied under the different Union legal frameworks. Appropriate cooperation should therefore be embedded within several provisions of this Directive, such as those regarding classification advice, supervision, or the development of guidelines.

(98) For products that combine a medicinal product and a medical device including an *in vitro* diagnostic medical device, the applicability of two regulatory frameworks, namely Regulation (EU) 2017/745[33] or (EU) 2017/746 of the European Parliament and of the Council[34], as applicable, should be specified and the appropriate interaction between this Directive and the two other applicable regulatory frameworks should be ensured. The same should apply to combinations of medical products with products other than medical devices.

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[33] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p. 1, ELI: http://data.europa.eu/eli/reg/2017/745/oj).

[34] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (OJ L 117, 5.5.2017, p. 176, ELI: http://data.europa.eu/eli/reg/2017/746/oj).

(99) To ensure that the competent authorities have all the information needed for their assessment in the case of integral combinations of a medicinal product with a medical device, or of combinations of a medicinal product with a product other than a medical device, the marketing authorisation applicant should submit data demonstrating the safe and effective use of the integral combination of the medicinal product with the medical device or of the combination of a medicinal product with the other product. The competent authority should assess the benefit-risk balance of the integral combination of the medicinal product with the medical device or of the combination of the medicinal product with the product other than a medical device, taking into account the suitability of the use of the medicinal product together with the medical device or with the other product.

(100) To ensure that the competent authorities of the Member States or the Agency, as applicable, have all the information needed for their assessment of medicinal products in exclusive use with a medical device or with an *in vitro* diagnostic medical device, that is to say, medicinal products that are presented in a package with a medical device or with an *in vitro* diagnostic medical device, or that are to be used with a medical device or with an *in vitro* diagnostic medical device referenced in the summary of product characteristics, the marketing authorisation applicant shall submit data demonstrating the safe and effective use of the medicinal product taking into account its use with the medical device or *in vitro* diagnostic medical device. The competent authorities of the Member States or the Agency, as applicable, should assess the benefit-risk balance of the medicinal product, taking into account the use of the medicinal product with the medical device or the *in vitro* diagnostic medical device.

(101) This Directive also clarifies that a medical device that is part of an integral combination of a medicinal product with a medical device should comply with the general safety and performance requirements set out in Annex I to Regulation (EU) 2017/745. A medicinal product in exclusive use with a medical device or with an *in vitro* diagnostic medical device needs to meet all of the requirements of Regulation (EU) 2017/745 or (EU) 2017/746, as applicable. If the action of a medicinal product in exclusive use with a medical device or with an *in vitro* diagnostic medical device is not ancillary to that of the medical device or the *in vitro* diagnostic medical device, the medicinal product should comply with the requirements of this Directive and of Regulation (EU) 2026/…[+] taking into account its use with the medical device or *in vitro* diagnostic medical device, without prejudice to the specific requirements of Regulation (EU) 2017/745 or (EU) 2017/746, as applicable.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(102) For integral combinations of a medicinal product with a medical device, medicinal products in exclusive use with a medical devices or with an *in vitro* diagnostic medical device and combinations of a medicinal product with a product other than a medical device, the competent authorities of the Member States or the Agency, as applicable, should also be able to request the marketing authorisation applicant to transmit any additional information needed and the marketing authorisation applicant should be bound to submit any such information requested. For medicinal products in exclusive use with a medical device or with an *in vitro* diagnostic medical device that is not ancillary to that of the medical device or the *in vitro* diagnostic medical device, the marketing authorisation applicant should also, upon request from the competent authorities of the Member States or the Agency, as applicable, submit any additional information relating to the medical device or *in vitro* diagnostic medical device, taking into account its use with the medicinal product, and that is relevant for the post-authorisation monitoring of the medicinal product, without prejudice to the specific requirements of Regulation (EU) 2026/…[+].

(103) For integral combinations of a medicinal product with a medical device and for combinations of a medicinal product with a product other than a medical device, the marketing authorisation holder should also bear the overall responsibility for the whole products in terms of compliance of the medicinal product with the requirements of this Directive and Regulation (EU) 2026/…[+] and should ensure coordination of the information flow between the sectors throughout the assessment procedure and the lifecycle of the medicinal product.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(104) In order to ensure the quality, safety and efficacy of medicinal products at all stages of manufacturing and distribution, the marketing authorisation holder should be responsible, when necessary, for tracing back an active substance, excipient or any other substance that is used in the manufacture of a medicinal product and intended to be part of the medicinal product or expected to be present in the medicinal product, for example impurities, degradation products or contaminants.

(105) In the interest of public health, marketing authorisation holders should be able to ensure the traceability of any substance that is used, intended or expected to be present in a medicinal product at all stages of manufacturing and distribution, and should be able to identify any natural or legal person from whom they have been supplied these substances. Therefore, procedures and systems should be put in place to provide that information where necessary to ensure the quality, safety or efficacy of medicinal products.

(106) It is recognised that the development of pharmaceuticals is an area where neither science, nor technology stand still. The last decades have seen new categories of medicinal products emerging, such as biological medicinal products, biosimilar medicinal products, advanced therapy medicinal products and, in the future, phage therapies. Those categories of products, in some instances, require adapted rules to fully take account of their specific characteristics. For that reason, a forward-looking legal framework should include provisions to enable such adapted frameworks subject to strict criteria and under a Commission empowerment guided by the scientific input of the Agency.

(107) The adaptations required for certain medicinal products or categories of medicinal products can entail specific requirements and targeted technical adaptations of the requirements compared to standard medicinal products. They could in particular include changes to the dossier requirements for such medicinal products, the way their quality, safety and efficacy is demonstrated by applicants or tailored manufacturing controls and good manufacturing practice requirements, as well as additional control methods prior and during their administration and use. Those adaptations should however not go beyond what is necessary for the attainment of the objective of adaptation to the specific characteristics or methods related to the medicinal product or category of medicinal products concerned.

(108) In order to increase preparedness and response capacity against health threats, in particular the emergence of antimicrobial resistance, adapted frameworks could prove useful in facilitating rapid changes to antimicrobials composition in order to preserve their efficacy. The use of established platforms would allow efficient and timely adaptation of those medicinal products to the clinical context.

(109) To optimise the use of resources for both marketing authorisation applicants and competent authorities and to avoid duplication of assessments of chemical active substances of medicinal products, marketing authorisation applicants should be able to rely on an active substance master file certificate or a certificate of suitability to the monograph of the European Pharmacopoeia, instead of submitting the relevant data as required in accordance with Annex II. It should be possible for an active substance master file certificate to be granted by the Agency in cases where the relevant data on the active substance concerned are not already covered by a monograph of the European Pharmacopoeia or by another active substance master file certificate. Where a certificate of suitability to a monograph of the European Pharmacopoeia or an active substance master file certificate is used as part of the marketing authorisation application, it should be possible to provide additional quality data that are not covered by those processes, as part of the marketing authorisation dossier to demonstrate the suitability of the active substance in the context of its intended use in the medicinal product. The Commission should be empowered to establish the procedure for the single assessment of an active substance master file. To further optimise the use of resources, the Commission should be empowered to allow the use of a certification scheme also for additional quality master files i.e. for active substances other than chemical active substances, or for other substances present or used in the manufacture of a medicinal product, required in accordance with Annex II, e.g. in the case of novel excipients, adjuvants, radiopharmaceutical precursors and active substance intermediates, when the intermediate is a chemical active substance by itself or used in combination with a biological substance.

(110) The concept of platform technology master files allows the reliance on data – encompassing aspects of quality, non-clinical, and clinical information – that have been pre-evaluated in the marketing authorisation application of a medicinal product. Platform technologies include, but are not limited to, viral and bacterial vector systems, recombinant protein-based methods, nucleic acid sequences, viral and bacterial vectors and synthetic biology approaches such as oligonucleotides and mRNA. The platform technology master file that documents the platform technology should be certified by the Agency to allow future uses. In the context of applying for marketing authorisations, products developed and manufactured using platform technology master files are to focus on the customisation of the platform to address the particular attributes of the medicinal product in question. This methodology avoids the duplication of assessments and minimizes the repetition of studies, thereby streamlining the development and regulatory evaluation processes for medicinal products. A fundamental requirement for the effective application of platform technology is the presence of a common dataset that remains applicable across medicinal products using the same technology. To qualify the use of a platform technology master file, applicants are obliged to demonstrate the applicability of the common dataset, substantiate the development and manufacturing platform, and furnish scientific justification that underscores the relevance of the platform data to the medicinal product in question. While the owner of a platform technology master file and the marketing authorisation holder are not necessarily the same, for example, some platform technologies can emanate from academic research and development, the marketing authorisation holder relying on a platform technology master file should retain full responsibility for its marketing authorisation, including the parts covered by the master file.

(111) For reasons of public health and legal consistency, and with a view to reducing the administrative burden and strengthening predictability for economic operators, variations of all types of marketing authorisations should be subject to harmonised rules.

(112) It should be possible for the terms of a marketing authorisation for a medicinal product to be varied after it has been granted. While the core elements of a variation are laid down in this Directive, the Commission should be empowered to complement those elements by laying down further necessary elements, to adapt the system to scientific and technological progress, including digitalisation, and to ensure that unnecessary administrative burden is avoided for both the marketing authorisation holders and the competent authorities of the Member States.

(113) The competent authorities of the Member States should have the power to evaluate additional evidence that can affect the benefit-risk balance of medicinal products, beyond what is provided by marketing authorisation holders. Where justified, the competent authorities of the Member States should be able to recommend that the marketing authorisation holder varies the terms of its marketing authorisation.

(114) Scientific and technological progress in data analytics and data infrastructure provide valuable support to the development, marketing authorisation and supervision of medicinal products. The digital transformation has affected regulatory decision-making, making it more data-driven and multiplying the possibilities for regulatory authorities to access evidence across the lifecycle of a medicinal product. This Directive recognises the competent authorities of the Member States' capacity to access and analyse data submitted independently from the marketing authorisation applicant or marketing authorisation holder. On that basis, the competent authorities of the Member States should take the initiative to recommend that the summary of product characteristics be updated in case new efficacy or safety data have an impact on the benefit-risk balance of a medicinal product.

(115) Access to individual patient data from clinical studies in structured format allowing for statistical analyses can assist regulators in understanding the submitted evidence and inform regulatory decision-making on the benefit-risk balance of a medicinal product. The introduction of such a possibility in the legislation is important to further enable data-driven benefit-risk assessments at all stages of the lifecycle of a medicinal product. This Directive therefore empowers competent authorities of Member States to request, as necessary, such data as part of the assessment of initial and post-marketing authorisation applications. Due to the sensitive nature of health data, the competent authorities should safeguard its processing operations and ensure that they respect the data protection principles of lawfulness, fairness and transparency, purpose limitation, data minimisation, accuracy, storage limitation, integrity and confidentiality. Where the processing of personal data is necessary for the purposes of this Directive, such processing should be done in accordance with Union law on the protection of personal data. Any processing of personal data under this Directive should take place in accordance with Regulations (EU) 2016/679[35] and (EU) 2018/1725[36] of the European Parliament and of the Council.

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[35] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (OJ L 119, 4.5.2016, p. 1, ELI: http://data.europa.eu/eli/reg/2016/679/oj).

[36] Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, and repealing Regulation (EC) No 45/2001 and Decision No 1247/2002/EC (OJ L 295, 21.11.2018, p. 39, ELI: http://data.europa.eu/eli/reg/2018/1725/oj).

(116) Pharmacovigilance rules are necessary for the protection of public health in order to prevent, detect and assess adverse reactions to medicinal products placed on the Union market, as the full safety profile of medicinal products can only be known after they have been placed on the market.

(117) In order to ensure the continued safety of medicinal products in use, it is necessary to ensure that pharmacovigilance systems in the Union are continually adapted to take account of scientific and technical progress.

(118) It is necessary to take account of changes arising as a result of international harmonisation of definitions, terminology and technological developments in the field of pharmacovigilance.

(119) The increasing use of electronic networks for communication of information on adverse reactions to medicinal products marketed in the Union is intended to allow competent authorities to share the information at the same time. In order to simplify the reporting of suspected adverse reactions, the marketing authorisation holders and the Member States should report those reactions only to the Union pharmacovigilance database and data-processing network referred to in Regulation (EU) 2026/…[+] (the 'Eudravigilance database'). The Eudravigilance database will be equipped to immediately forward reports on suspected adverse reactions received from marketing authorisation holders to the Member States on whose territory the reaction occurred. It should be possible for the Agency, in consultation with the Commission, Member States and marketing authorisation holders, to draw up and publish a detailed guide regarding the monitoring of relevant adverse reaction databases maintained outside the Union and the entry of relevant information from those databases into the Eudravigilance database.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(120) Member States and marketing authorisation holders should operate a pharmacovigilance system to collect information that is useful for the monitoring of medicinal products, including information on suspected adverse reactions arising from use of a medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, including off-label use, overdose, misuse, abuse and medication errors by patients and healthcare professionals. Mistakes in the prescribing, dispensing, storing, preparation and administration of a medicine are common types of medication errors. Suspected adverse reactions should be recorded and reported by Member States and marketing authorisations holders to the Eudravigilance database for the monitoring of safety of medicinal products. The reports should be part of the continuous evaluation of the benefit-risk balance of the medicinal products. Summaries of data relevant to the benefit-risk balance should be included in periodic safety update reports. Marketing authorisation holders should also record and report information on adverse reactions occurring in the context of post-authorisation studies, including post-authorisation studies in specific populations such as children, for evaluation of the benefit-risk balance.

(121) It is the interest of the Union to ensure that the pharmacovigilance systems for centrally authorised medicinal products and those authorised by other procedures are consistent.

(122) Marketing authorisation holders should be proactively responsible for on-going pharmacovigilance of the medicinal products they place on the market including for an appropriate period after the marketing authorisation has been withdrawn or revoked.

(123) The use of colours in human and veterinary medicinal products is currently regulated by Directive 2009/35/EC of the European Parliament and of the Council[37] and is restricted to those authorised in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council[38], for which specifications are laid down in Commission Regulation (EU) No 231/2012[39]. The use of excipients other than colours in medicinal products is subject to the Union rules on medicinal products and is evaluated as part of the overall benefit-risk profile of a medicinal product.

(124) Experience has shown the need to maintain to a certain extent the principle of the use in medicinal products of those colours authorised as food additives. However, it is also appropriate to provide for a specific assessment of the use of a colour in medicinal products when a food additive is removed from the Union list of authorised food additives. Therefore, in this specific case, the Agency should carry out its own assessment of the use of the colour concerned in medicinal products, taking into account the European Food Safety Authority opinion and its underlying scientific evidence, as well as any additional scientific evidence and giving particular consideration to the use of the colour concerned in medicinal products. The Agency should also be responsible for following any scientific evidence for the colours retained for specific medicine use only. Directive 2009/35/EC should therefore be repealed.

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37 Directive 2009/35/EC of the European Parliament and of the Council of 23 April 2009 on the colouring matters which may be added to medicinal products (OJ L 109, 30.4.2009, p. 10, ELI: http://data.europa.eu/eli/dir/2009/35/oj).

38 Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives (OJ L 354, 31.12.2008, p. 16, ELI: http://data.europa.eu/eli/reg/2008/1333/oj).

39 Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council (OJ L 83, 22.3.2012, p. 1, ELI: http://data.europa.eu/eli/reg/2012/231/oj).

(125) With regard to supervision and inspections, manufacturing and import of excipients, functional excipients, starting materials or intermediate products should be under surveillance due to their possible ancillary action on the active substance and to their possible impact on the quality, safety and efficacy of the medicinal products.

(126) The main purpose of any regulation on the manufacture and distribution of medicinal products is to safeguard public health.

(127) Manufacturing and wholesale distribution authorisations are to be subject to certain essential conditions and it is the responsibility of the Member State concerned to ensure that such conditions are met; each Member State is to recognise authorisations granted by other Member States.

(128) It should be ensured that, in the Member States, the supervision and control of the manufacture and the distribution of medicinal products are carried out by official representatives of the competent authority who fulfil minimum conditions of qualification.

(129) There may be cases where manufacturing activities, including testing, of medicinal products need to take place in sites close to patients, taking into account the specific properties of the medicinal product as well as considerations related to its quality, safety and efficacy, for example advanced therapy medicinal products with a short shelf-life or where proximity to the patient being treated or customisation for an individual patient is to the patient's benefit. In such cases, it can be necessary for manufacturing to be decentralised to multiple sites to reach patients across the Union. The use of decentralised manufacturing should be approved during the marketing authorisation procedure where deemed appropriate by the competent authority of the Member State or the Agency. Where the manufacturing steps are decentralised, they should be carried out under the responsibility of the qualified person of an authorised central site. The decentralised sites should not be required to obtain a manufacturing authorisation separate from the one granted to the relevant central site but should be registered by the competent authority of the Member State in which the decentralised site is located and supervised by that authority. In the case of medicinal products containing, consisting of or derived from SoHO, the decentralised sites are to be registered as SoHO entities as defined in and in accordance with Regulation (EU) 2024/1938 for the activities of donor review and eligibility assessment, donor testing and collection, where applicable. In respect of decentralised sites falling within the scope of this Directive and engaging in activities covered by other Union legal acts, in order to ensure their effective functioning, the competent authorities of the Member States supervising the central site and the decentralised sites should cooperate and exchange information with the authorities supervising those activities under other Union legal acts. This cooperation should, where appropriate, pertain to the coordination of authorisation, registration and supervision activities, including joint inspections, related to the central site and the decentralised sites, aiming to ensure efficiency of those activities.

(130) The quality of medicinal products manufactured or available in the Union should be guaranteed by requiring that the active substances used in their composition comply with the principles of good manufacturing practice in relation to those medicinal products.

(131) Verification of compliance with the legal requirements of manufacturing, distribution and use of medicinal products by relevant entities through a system of supervision, is of fundamental importance to ensure that the objectives of this Directive are effectively achieved. Therefore, the competent authorities of the Member States should be empowered to perform on site or remote inspections, as part of the system of supervision at all stages of manufacturing, distribution and use of medicinal products or active substances. It has proved necessary to reinforce the Union provisions on inspections and to compile a Union database of the results of those inspections. The competent authorities of the Member States should have the possibility to rely on the outcome of inspections conducted by trusted non-Union regulatory authorities. To preserve the effectiveness of the inspections, the competent authorities should also have the possibility to perform joint inspections and also, where necessary, unannounced inspections.

(132) The frequency of controls should be established by the competent authorities having regard to the risk and to the level of compliance expected in different situations. That approach should allow those competent authorities to allocate resources where the risk is highest. In some cases, the system of supervision should be applied irrespective of the level of risk or suspected non-compliance, for example in the context of granting manufacturing authorisations.

(133) Within the procedure for ‘Certification of Suitability to the monographs of the European Pharmacopoeia’, the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe is to verify, by means of inspections, whether the data submitted by the applicant confirms the suitability of monographs to control the chemical purity, microbiological quality and, if relevant, Transmissible Spongiform Encephalopathy risk. It is also to verify whether the manufacturing complies with good manufacturing practice for active substances. Depending on the outcome of the inspection, a certificate of compliance or non-compliance with good manufacturing practice is issued by the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe or by the Member State participating in the inspection.

(134) Each undertaking that manufactures or imports medicinal products should set up a mechanism to ensure that all information supplied about a medicinal product is in conformity with the approved conditions of use.

(135) The conditions governing the supply of medicinal products to the public should be harmonised.

(136) In relation to the supply of medicinal products to the public, persons moving around within the Union have the right to carry a reasonable quantity of medicinal products lawfully obtained for their personal use. It should also be possible for a person established in one Member State to obtain a reasonable quantity of medicinal products from another Member State, where those products are intended for that person’s personal use.

(137) Pursuant to Regulation (EU) 2026/…[+], certain medicinal products are subject to a centralised marketing authorisation. In this context, the prescription status of medicinal products covered by a centralised marketing authorisation needs to be established. It is therefore important to set the criteria on the basis of which Union decisions will be taken.

(138) It is also appropriate to harmonise the basic principles applicable to the prescription status of medicinal products in the Union or in the Member State concerned, while taking as a starting point the principles already established on this subject by the Council of Europe as well as the work of harmonisation completed within the framework of the United Nations Single Convention on narcotic drugs of 1961 and the United Nations Convention on Psychotropic Substances of 1971.

(139) Many operations involving the wholesale distribution of medicinal products can cover several Member States simultaneously.

(140) It is necessary to exercise control over the entire chain of distribution of medicinal products, from their manufacture or import into the Union through to their supply to the public, so as to guarantee that such products are stored, transported and handled in suitable conditions. The requirements that should be adopted for this purpose will considerably facilitate the withdrawal of defective products from the market and allow more effective efforts against counterfeit products.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(141) Any person involved in the wholesale distribution of medicinal products should be in possession of a special authorisation. Pharmacists and other persons authorised to supply medicinal products to the public, who confine themselves to that activity, should be exempt from obtaining a special authorisation. It is however necessary, in order to control the complete chain of distribution of medicinal products, that pharmacists and other persons authorised to supply medicinal products to the public keep records showing transactions in products received.

(142) Certain Member States impose certain public service obligations on wholesale distributors who supply medicinal products to pharmacists and on other persons authorised to supply medicinal products to the public. Those Member States should be able to continue to impose those obligations on wholesale distributors established within their territory. They should also be able to impose them on holders of a wholesale distribution authorisation that has been granted by another Member State on condition that they do not impose any obligation more stringent than those that they impose on their own wholesale distributors and provided that such obligations can be regarded as justified on grounds of public health protection and are proportionate in relation to the objective of such protection.

(143) Rules should be laid down as to how the labelling and package leaflets are to be presented. The package leaflet should be accessible, easily legible, clearly comprehensible by users, including especially the target patient groups, and indelible. Design choices should primarily serve function and readability, rather than aesthetics.

(144) The provisions governing the information supplied to users should provide a high degree of consumer protection, so that medicinal products are used correctly on the basis of full and comprehensible information.

(145) The placing on the market of medicinal products the labelling and package leaflet of which comply with this Directive should not be prohibited or impeded on grounds connected with the labelling or package leaflet.

(146) The use of electronic and technological possibilities for package leaflets other than in paper format can facilitate access to medicinal products and medicinal products distribution. It should always guarantee equal quality of information to all patients compared to product information in paper format. It can additionally enable other forms of transmission of such information to persons with sensory impairments, for example through audiovisual or other means.

(147) Member States have varying levels of digital literacy and internet access. In addition, patient and healthcare professional needs can differ. It is therefore necessary that Member States have discretion with respect to the adoption of measures allowing package leaflets to be made available exclusively electronically for specific categories of medicinal products or for all medicinal products while ensuring that no patient is left behind, taking into account the needs of different age categories and the different levels of digital literacy in the population, and making sure that product information is easily accessible to all patients. Member States should, where appropriate, consider allowing package leaflets to be made available only electronically, while ensuring full compliance with the rules on protection of personal data, notably with Regulation (EU) 2016/679, and should prevent the identification, profiling or tracking of individuals and should adhere to harmonised standards developed at EU level.

(148) Where Member States decide that the package leaflet should be made available only electronically, the marketing authorisation holders concerned should ensure that a paper version of the package leaflet is made available to patients upon request and free of charge. Marketing authorisation holders should also ensure adherence to all specifications, common standards and formats specified by the relevant implementing acts and guidance and that the information in digital format is easily accessible to all patients, for instance by including on the outer packaging of the product a digitally readable element, for example a QR code, a data matrix code, a barcode, or any other appropriate technology which would direct the patient to the electronic version of the package leaflet in a simple, user friendly and effective manner.

(149) The use of multi-country packages that are also multilingual can be a tool for access to medicinal products, in particular for small markets and in public health emergencies. Where such packages are used, it should be possible for Member States to also allow the use on the labelling and package leaflet of an official language of the Union that is commonly understood in the Member States where the multi-country package that is also multilingual is marketed.

(150) Security of supply in Malta continues to be hindered by the low availability of medicinal products with package leaflets in the official languages of that Member State. For this reason, it is appropriate to allow for the competent authorities of Malta to maintain in force marketing authorisations that were granted, extended or maintained in accordance with Article 126c of Directive 2001/83/EC and that are valid at the time of entry into force of this Directive until after the rules on electronic product information become applicable in all Member States, taking also into account the deferred application of those rules for medicinal products already placed on the market.

(151) To ensure a high level of transparency of public support to the research and development of medicinal products, the reporting of any public contribution to the development of a particular medicinal product should be a requirement for all medicinal products. Given however the practical difficulty to identify how indirect public funding instruments, such as tax advantages, have supported a particular medicinal product, the reporting obligation should only concern the direct public financial support, such as direct grants or contracts, received from any public authority, publicly funded body, philanthropic organisation, or not-for-profit organisation or fund. Therefore, the provisions of this Directive ensure, without prejudice to the rules on the protection of confidential and personal data, transparency regarding any direct financial support received from any public authority or publicly funded body, philanthropic organisation, or not-for-profit organisation or fund to carry out any activities for the research and development of medicinal products.

(152) To ensure the accuracy of the information on public financial support made publicly available by the marketing authorisation holder, that information should be subject to an audit by an independent external auditor.

(153) In order to ensure a harmonised and consistent reporting of any public contribution to the development of a particular medicinal product, the Commission should adopt implementing acts to lay down the principles and format to which the marketing authorisation holder should adhere when reporting that information.

(154) This Directive is without prejudice to the application of measures adopted pursuant to Directive 2006/114/EC of the European Parliament and of the Council[40] or pursuant to Directive 2005/29/EC of the European Parliament and of the Council[41]. Therefore, the provisions of this Directive regarding the advertising of medicinal products should be considered, where relevant, as a *lex specialis* with respect to Directive 2005/29/EC.

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40 Directive 2006/114/EC of the European Parliament and of the Council of 12 December 2006 concerning misleading and comparative advertising (OJ L 376, 27.12.2006, p. 21, ELI: http://data.europa.eu/eli/dir/2006/114/oj).

41 Directive 2005/29/EC of the European Parliament and of the Council of 11 May 2005 concerning unfair business-to-consumer commercial practices in the internal market and amending Council Directive 84/450/EEC, Directives 97/7/EC, 98/27/EC and 2002/65/EC of the European Parliament and of the Council and Regulation (EC) No 2006/2004 of the European Parliament and of the Council ('Unfair Commercial Practices Directive') (OJ L 149, 11.6.2005, p. 22, ELI: http://data.europa.eu/eli/dir/2005/29/oj).

(155) Advertising of medicinal products, even of medicinal products not subject to medical prescription, could affect public health and distort competition. Therefore, the advertising of medicinal products should meet certain criteria. Persons qualified to prescribe, administer or supply medicinal products can properly evaluate the information available in advertising because of their knowledge, training and experience. The advertising of medicinal products to persons who cannot properly assess the risk associated with their use can lead to medicinal product misuse or overconsumption which is liable to harm public health. Therefore, the advertising to the general public of medicinal products that are available on medical prescription only should be prohibited. Furthermore, distribution of samples free of charge to the general public for promotional ends is to be prohibited, also teleshopping for medicinal products is prohibited under Directive 2010/13/EU of the European Parliament and of the Council[42]. It should be possible, under certain restrictive conditions, to provide samples of medicinal products free of charge to persons qualified to prescribe or supply them so that they can familiarise themselves with new products and acquire experience in dealing with them.

[42] Directive 2010/13/EU of the European Parliament and of the Council of 10 March 2010 on the coordination of certain provisions laid down by law, regulation or administrative action in Member States concerning the provision of audiovisual media services (Audiovisual Media Services Directive) (OJ L 95, 15.4.2010, p. 1, ELI: http://data.europa.eu/eli/dir/2010/13/oj).

(156) The advertising of medicinal products should aim to disseminate objective and unbiased information about the medicinal product. For that purpose, it is expressly forbidden to highlight negatively another medicinal product or to suggest that an advertised medicinal product might be safer or more effective than another medicinal product. Comparison of medicinal products should only be allowed if it is based on information that is supported objectively by the summaries of product characteristics of the medicinal products concerned. This prohibition covers any medicinal product, including biosimilar medicinal products, and therefore it would be misleading to suggest, in the advertisement, that a biosimilar medicinal product would not be interchangeable with the original biological medicinal product or another biosimilar medicinal product similar to the same original biological medicinal product. Additional strict rules about negative and comparative advertising of competitor medicinal products should aim to prohibit claims that can mislead persons qualified to prescribe, administer or supply them.

(157) The dissemination of information which encourages the purchase of medicinal products should be considered to fall under the concept of advertising of medicinal products, even where that information does not refer to a specific medicinal product but refers to unspecified medicinal products.

(158) The advertising of medicinal products should be subject to strict conditions and effective, adequate monitoring. Reference in this regard should be made to the monitoring mechanisms set up by Directive 2006/114/EC.

(159) Medical sales representatives have an important role in the promotion of medicinal products. Therefore, certain obligations should be imposed upon them, in particular the obligation to supply the person visited with a summary of product characteristics.

(160) Even minimal inducement can result in biased decisions with regard to prescription behaviour by physicians. Therefore, to avoid conflicts of interest, in the absence of national rules governing the disclosure of transfers of value, Member States should establish and maintain a publicly available list of links to the disclosure platforms operated by trade associations or by marketing authorisation holders for the reporting of transfers of value related to the advertising activities.

(161) Innovative, combination medicinal products and other developed medicinal products are complex as regards their composition and administration. Therefore, people who are qualified to administer medicinal products, as well as people who are qualified to prescribe such products, need to be familiar with all the characteristics of those medicinal products, in particular their safe administration and use, including comprehensive instructions for patients. For that purpose, providing information about medicinal products subject to medical prescription to persons qualified to administer them is also clearly allowed.

(162) Persons qualified to prescribe, administer or supply medicinal products should have access to a neutral, objective source of information about products available on the market. It is nevertheless for the Member States to take all measures necessary to this end, in the light of their own particular situation.

(163) In order to avoid waste, reduce the burden on the environment, mitigate shortages and realise cost savings, it is feasible to allow re-dispensing of medicinal products, under strict conditions. Through the practice of re-dispensing, a pharmacy can take back and re-dispense a medicinal product that has already been supplied to a patient. Member States should ensure that re-dispensing can only be done by the same pharmacy that initially supplied the medicinal product. A pharmacy should only be allowed to re-dispense medicinal products to an individual patient identified by name, on the basis of informed consent. The returned medicinal products should be allowed to be re-dispensed only after the pharmacy has verified that the medicinal product concerned is not a falsified medicinal product, that the expiry date has not passed and that the medicinal product has been stored under appropriate conditions. To check these parameters, instruments such as a tamper-proof bag and temperature logger can be used. The pharmacy should record the medicinal product and the recipient for the purpose of inspections. Re-dispensing might not be feasible for all medicinal products. Member States should be able to identify and list in national legislation which specific medicinal products are allowed to be re-dispensed in that Member State, such as oral oncological medicinal products, which could provide for a pilot category. Member States should lay down rules on liability for potential harm resulting from the use of the medicinal products that have been re-dispensed when such harm is a consequence of a failure to ensure appropriate storage or transport conditions between the initial dispensing of the medicinal product and its return to the pharmacy, or a failure to ensure that the medicinal product re-dispensed has not been falsified. This provision should not affect the possibility for Member States to set additional restrictive conditions under which medicinal products can be re-dispensed. Member States should ensure that the collection and re-dispensing of medicinal products are not used for obtaining economic gains and allowing penetration of the re-dispensed medicinal products to the supply chain.

(164) In order to ensure that information on the use of the medicinal products in children are appropriately taken into account at the moment of marketing authorisation, it is necessary to introduce a requirement for new medicinal products or when developing paediatric indications of already authorised medicinal products covered by a patent or a supplementary protection certificate, to present either the results of studies in the paediatric population in accordance with an agreed paediatric investigation plan or proof of having obtained a waiver or deferral, at the time of submitting a marketing authorisation application or an application for a new therapeutic indication, new pharmaceutical form or new route of administration. In order to ensure that the data supporting the marketing authorisation concerning the use of a medicinal product in children are adequate, the competent authorities responsible for the authorisation of a medicinal product should check that the studies conducted comply with the agreed paediatric investigation plan or whether any waivers or deferrals have been granted, when validating the marketing authorisation applications.

(165) To provide healthcare professionals and patients with information on the safe and effective use of medicinal products in the paediatric population, the results of the studies conducted in accordance with a paediatric investigation plan, irrespective of whether or not those results support the use of the medicinal product in children, should be included in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product. Information on waivers should also be included in the product information. When all the measures provided for in the paediatric investigation plan have been complied with, that fact should be recorded in the marketing authorisation, and that should then be the basis upon which companies can obtain rewards.

(166) Relevant data and information collected through clinical studies conducted before the introduction in the Union of a paediatric medicines Regulation and received by the competent authorities should be assessed without undue delay and taken into consideration for eventual variations of existing marketing authorisations.

(167) In order to ensure uniform conditions for the implementation of this Directive, implementing powers should be conferred on the Commission in order to: lay down details of the application for a hospital exemption approval, specify the content and format for the collection and reporting of data on ATMPs prepared under hospital exemption, lay down the practical arrangements for the exchange of knowledge between holders of a hospital exemption approval and the modalities for the preparation and use of ATMPs under hospital exemption, on a non-routine basis; set out the content and format of the request to use decentralised manufacturing and specify the application of decentralised manufacturing; establish a list of colours permitted for use in medicinal products other than those included in the Union list of authorised food additives and adopt decisions as to whether a colour is to be added to that list; adopt decisions on applications, after receiving the opinion of the Committee for Medicinal Products for Human Use or the position of the majority of the Member States represented within the coordination group, as applicable, and after obtaining the opinion of the Standing Committee on Medicinal Products for Human Use, in particular, in the event of divergent positions of Member States in a decentralised or mutual recognition procedure or in relation to the harmonisation of summary of product characteristics, in the event of divergent decisions by Member States concerning a national marketing authorisation, its variation, suspension or revocation or the summary of product characteristics, or in the event of divergent positions of Member States in the context of the Union interest referral or the urgent Union procedure or the procedure for regulatory action on periodic safety update reports or following the submission of a final study report on a non-interventional post-authorisation safety study; lay down the principles and format for the information on the public financial support received to be reported;

establish common standards and formats for the electronic version of the package leaflet, the summary of product characteristics and the labelling, establish criteria for the provision of such product information through secure digital platforms and services and for the provision, establishment, management and accessibility of such digital platforms and services, establish the procedures to validate the electronic version of the package leaflet and to make it available to patients, specify information on the packaging on how to access this electronic version and specify the details on how to include the commonly recognised global antimicrobial resistance symbol in the package leaflet and information on antimicrobial resistance and the importance of appropriate use and disposal of antimicrobials; harmonise the performance of the pharmacovigilance activities provided for in this Directive by setting out the content and rules on the maintenance of the pharmacovigilance system master file, minimum requirements for the quality system for the performance of pharmacovigilance activities, rules on the use of internationally agreed terminology, formats and standards for the performance of such activities, minimum requirements for the monitoring of data in the Eudravigilance database, the format and content of the electronic transmission of suspected adverse reactions and the format and content of electronic periodic safety update reports and risk management plans, the format of protocols, abstracts and final study reports for the non-interventional post-authorisation safety studies; establish a list of herbal substances, herbal preparations and combinations thereof for use in traditional herbal medicinal products; include a third country in a list after assessing its regulatory framework applicable to active substances exported to the Union and apply the relevant requirements; and specify the design and the technical, electronic and cryptographic requirements for verification of the authenticity of the common logo that is to be displayed on the website relating to the offer for sale at a distance to the public of medicinal products. Those powers should be exercised in accordance with Regulation (EU) No 182/2011 of the European Parliament and of the Council[43].

[43] Regulation (EU) No 182/2011 of the European Parliament and of the Council of 16 February 2011 laying down the rules and general principles concerning mechanisms for control by Member States of the Commission's exercise of implementing powers (OJ L 55, 28.2.2011, p. 13, ELI: http://data.europa.eu/eli/reg/2011/182/oj).

(168) Due to the need to reduce the overall time taken to authorise medicinal products, the time between the opinion of the Committee for Medicinal Products for Human Use and any final decision from the Commission concerning national marketing authorisations, in particular for referrals, should be reduced, in principle, to 46 days.

(169) On the basis of the opinion of the Committee for Medicinal Products for Human Use, the Commission should adopt a draft decision on the referral or the application concerned. In duly justified cases, it should be possible for the Commission to refer the opinion of the Committee for Medicinal Products for Human Use or the position of the majority of the Member States represented within the coordination group back to the Agency or to the coordination group, as applicable, for further consideration. The Commission's draft decision may diverge from the opinion of the Committee for Medicinal Products for Human Use. The Commission should adopt its final decision by means of implementing acts after obtaining the opinion of the Standing Committee on Medicinal Products for Human Use. Taking into account the need to make medicinal products swiftly available to patients, it should be acknowledged that the chairperson of the Standing Committee on Medicinal Products for Human Use is to use the available mechanisms under Regulation (EU) No 182/2011 and notably the possibility to obtain the Committee's opinion by written procedure and within expeditious deadlines, which, in principle, do not exceed 10 calendar days.

(170) The power to adopt acts in accordance with Article 290 TFEU should be delegated to the Commission in respect of adopting any necessary changes to Annex II in order to take into account scientific and technical progress; amending Annexes I to VI in order to adapt them to scientific and technical progress as well as amending the ERA requirements as regards the obligation to indicate whether the medicinal product or any of its ingredients or constituents is an endocrine active agent or has been assigned to hazard classes referred to in this Directive, the obligation to include in the ERA risk mitigation measures to avoid or limit emissions in the environment of ingredients and constituents of medicinal products listed as pollutants in specific Union legislation and to explain how such measures can address the identified risks to the environment, the obligation to include in the ERA for antimicrobials an evaluation of the risk for antimicrobial resistance selection in the environment due to the manufacturing supply chain, use and disposal of the antimicrobial and the obligation to update the ERA with any relevant information, including relevant information from environmental monitoring, eco-toxicity studies, risk assessments under other Union legal acts and environmental exposure data or, for specified ERAs, with information that has been identified as missing concerning medicinal products that are potentially harmful to the environment; amending the list of labelling particulars in Annex IV in order to take account of scientific progress or patients' needs; amending the list of medicinal products and categories of medicinal products in Annex VII in order to take account of scientific and technical progress; amending certain definitions in order to take account of technical and scientific progress and taking into account definitions agreed at Union and international level without amending the scope of the definitions; and amending the requirements as regards the degree of dilution of a homeopathic medicinal product to guarantee its safety as laid down in this Directive in order to take account of scientific progress.

It is of particular importance that the Commission carry out appropriate consultations during its preparatory work, including at expert level, and that those consultations be conducted in accordance with the principles laid down in the Interinstitutional Agreement of 13 April 2016 on Better Law-Making. In particular, to ensure equal participation in the preparation of delegated acts, the European Parliament and the Council receive all documents at the same time as Member States' experts, and their experts systematically have access to meetings of Commission expert groups dealing with the preparation of delegated acts.

(171) The power to adopt acts in accordance with Article 290 TFEU should be delegated to the Commission in order to supplement certain non-essential elements of this Directive in respect of specifying the content and format of ERA monographs, the procedures for adopting and updating the ERA monographs, the procedures for submission of information, studies and data, the risk-based criteria for the selection and prioritisation of active substances in relation to ERA monographs and the use of ERA monographs in the context of new marketing authorisation applications for medicinal products to support the ERA for those medicinal products; specifying the procedure for the examination of an application for an active substance master file certificate, the publication of such certificates, the procedure for making changes to the active substance master file and its certificate, and the rules on access to the active substance master file and its assessment report; specifying additional quality master files to provide information on a constituent of a medicinal product, the procedure for the examination of an application for a quality master file certificate, the publication of such certificates, the procedure for making changes to the quality master file and its certificate, and the rules on access to the additional quality master file and its assessment report; identifying the substances to which the provisions on additional quality master file apply; determining the situations in which post-authorisation efficacy studies may be required; laying down the adapted framework for medicinal products and categories of medicinal products listed in Annex VII as well as the documentation to be submitted in that regard; setting out a reduced list of mandatory labelling particulars outlined in Annex IV that shall appear on the outer packaging of multi-country packages that are also multilingual; laying down detailed rules for the safety features in Annex IV setting out the characteristics and technical specifications of the unique identifier of the safety features that enables the authenticity of medicinal products to be verified and individual packs to be identified; and setting out the lists of medicinal products or categories of medicinal products subject to medical prescription that are not to bear the safety features and those not subject to medical prescription that are to bear the safety features;

specifying exemptions from the variation procedure and the categories in which variations should be classified and establishing procedures for the examination of applications for variations to the terms of marketing authorisations as well as specifying conditions and procedures for cooperation with third countries and international organisations for examination of applications for such variations; specifying the criteria and the verifications in relation to the assessment of the potential falsified character of medicinal products; specifying the annual notification to be made by the qualified person to the competent authority of the Member State where a decentralised site is located, on the inventory of the changes that have taken place as regards the information provided in the registration form relating to that decentralised site; specifying the principles of good manufacturing and good distribution practices for medicinal products and active substances, in line with other principles of good practice established under any other Union legal framework, as well as the rules applicable to excipients as regards the formalised risk assessment for ascertaining the appropriate good manufacturing practice taking into account requirements under other appropriate quality systems as well as the source and intended use of the excipients and previous instances of quality defects; and laying down the principles applicable to the system of supervision, the joint inspections, the exchange of information and cooperation in the coordination of inspections in the system of supervision and the trusted non-Union regulatory authorities. It is of particular importance that the Commission carry out appropriate consultations during its preparatory work, including at expert level, and that those consultations be conducted in accordance with the principles laid down in the Interinstitutional Agreement of 13 April 2016 on Better Law-Making. In particular, to ensure equal participation in the preparation of delegated acts, the European Parliament and the Council receive all documents at the same time as Member States' experts, and their experts systematically have access to meetings of Commission expert groups dealing with the preparation of delegated acts.

(172) This Directive seeks to enable the right of access to preventive healthcare and the right to benefit from medical treatment under the conditions established by national laws and practices and to ensure a high level of human health protection in the definition and implementation of all Union policies and activities as laid down in Article 35 of the Charter of Fundamental Rights of the European Union.

(173) Since the objectives of this Directive, namely to establish rules on medicinal products ensuring the protection of public health and the environment as well as the functioning of the internal market, cannot be sufficiently achieved by the Member States as national rules would lead to disharmonisation, unequal patient access to medicinal products and barriers to the internal market, but can rather, by reason of their effects, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union. In accordance with the principle of proportionality as set out in that Article, this Directive does not go beyond what is necessary in order to achieve those objectives.

(174) The European Data Protection Supervisor was consulted in accordance with Article 42(1) of Regulation (EU) 2018/1725 and delivered an opinion on 19 June 2023.

(175) In accordance with the Joint Political Declaration of 28 September 2011 of Member States and the Commission on explanatory documents[44], Member States have undertaken to accompany, in justified cases, the notification of their transposition measures with one or more documents explaining the relationship between the components of a directive and the corresponding parts of national transposition instruments. With regard to this Directive, the legislator considers the transmission of such documents to be justified,

HAVE ADOPTED THIS DIRECTIVE:

[44] OJ C 369, 17.12.2011, p. 14.

Chapter I

Subject matter, scope and definitions

Article 1

Subject matter and scope

1. This Directive lays down rules for the placing on the market, manufacturing, import, export, supply, distribution, pharmacovigilance, advertising, supervision, control and use of medicinal products for human use.

2. This Directive applies to medicinal products for human use intended to be placed on the market.

3. In addition to the medicinal products referred to in paragraph 2, Chapter XI applies also to starting materials, active substances, excipients and intermediate products.

4. Where a product that falls within the definition of a medicinal product under this Directive is also covered by a definition in another Union legal act, and there is a conflict between the rules applicable to that product under this Directive and under that other Union legal act, the rules set out in this Directive shall prevail.

5. Except for Article 2, this Directive does not apply to:

(a) medicinal products prepared in a pharmacy in accordance with a medical prescription or, where provided for in national law, with a written instruction of a doctor, to meet the special needs of an individual patient ('magistral formulas');

(b) medicinal products prepared in a pharmacy in accordance with a pharmacopoeia and intended to be supplied directly to the patients served by the pharmacy in question ('officinal formulas').

Magistral formulas or officinal formulas shall not include medicinal products listed in points 1 and 2 of Annex I to Regulation (EU) 2026/…[+].

6. This Directive does not apply to:

(a) investigational medicinal products as defined in Article 2(2), point (5), of Regulation (EU) No 536/2014;

(b) substances of human origin (SoHO), unless they fall within the definition of an advanced therapy medicinal product (ATMP) or a SoHO-derived medicinal product other than ATMPs.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

7. Without affecting the rules set out in Regulation (EU) 2024/1938, including as regards the principle of voluntary and unpaid donations, this Directive and all Regulations referred to in this Directive shall be without prejudice to the application of national legislation prohibiting or restricting the use of any specific type of SoHO or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from such substances or cells, on grounds not covered by this Directive or those Regulations.

Member States shall communicate such national legislation to the Commission.

8. This Directive shall not affect the powers of the Member States' authorities either as regards the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes on the basis of health, economic or social conditions.

9. This Directive shall not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products as contraceptives or abortifacients.

Member States shall communicate such national legislation to the Commission.

Article 2

Magistral formulas and officinal formulas

1. A Member State may allow a pharmacy to supply officinal formulas to a hospital served by it upon the request of that hospital.

Such supply shall be subject to the approval of the competent authority of the Member State concerned.

2. Where necessary to ensure the availability of a magistral formula to meet the special needs of individual patients, Member States may allow pharmacies to prepare magistral formulas in advance when duly justified, on the basis of anticipated medical prescriptions or instructions, as relevant, for such patients.

In such cases, the magistral formula shall be prepared for:

(a) up to the following seven days; or

(b) when duly justified and taking into account the properties of the medicinal product, up to the following three weeks.

Member States shall ensure that pharmacies keep a record of magistral formulas prepared in advance in accordance with this paragraph, including the justifications therefor, and that the relevant documentation is readily available for inspection.

Article 3

ATMPs prepared under hospital exemption

1. By way of derogation from Article 1(1), only this Article applies to ATMPs prepared within a Member State on a non-routine basis in accordance with the requirements referred to in paragraph 3 of this Article and used within that Member State in a hospital under the exclusive professional responsibility of a medical practitioner in order to comply with an individual medical prescription for a custom-made product to meet the needs of an individual patient (‘ATMPs prepared under hospital exemption’).

2. Member States shall ensure that the manufacture and use of an ATMP prepared under hospital exemption require the approval of the competent authority of the Member State ('hospital exemption approval'). Member States shall notify any such approval, as well as subsequent changes thereto, to the Agency.

The application for a hospital exemption approval shall be submitted to the competent authority of the Member State where the hospital is located.

3. Member States shall ensure that ATMPs prepared under hospital exemption comply with requirements that are equivalent to the good manufacturing practice and the traceability requirements for ATMPs referred to in Article 163 of this Directive and in Article 15 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council[45] respectively, and with pharmacovigilance requirements that are equivalent to those provided for at Union level pursuant to Regulation (EU) 2026/…[+].

4. Member States shall ensure that data on the use, safety and efficacy of ATMPs prepared under hospital exemption, as well as any relevant data specified in the implementing acts referred to in paragraph 7, are collected and reported by the holder of the hospital exemption approval to the competent authorities of the Member States at least annually. The data shall be collected and reported in a structured and standardised way that ensures robust, reliable and comparable results and conclusions.

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[45] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121, ELI: http://data.europa.eu/eli/reg/2007/1394/oj).

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

The competent authorities of the Member States shall review the data and shall verify the compliance of the ATMPs prepared under hospital exemption with the requirements referred to in paragraph 3.

Upon request, the competent authorities of the Member States or the Agency shall provide scientific and regulatory advice to developers of ATMPs for preparation and use under hospital exemption and to holders of a hospital exemption approval on the further development of their ATMPs and, where appropriate, for the purpose of obtaining a marketing authorisation granted by the Union.

5. If a hospital exemption approval is revoked due to safety or efficacy concerns the competent authority of the Member State that approved the hospital exemption shall inform the Agency. The Agency shall inform the competent authorities of the other Member States.

6. The competent authority of the Member State that approved the hospital exemption shall transmit the data related to the use, safety and efficacy of the ATMP prepared under hospital exemption to the Agency annually. The Agency shall, in collaboration with the competent authorities of Member States and the Commission, set up and maintain a repository of those data, including a mechanism for electronic submission.

7. The Commission shall adopt implementing acts to specify the following:

(a) details of the application for a hospital exemption approval referred to in paragraph 2, second subparagraph, including the evidence on quality, safety and efficacy of the ATMPs prepared under hospital exemption for the approval and the subsequent changes;

(b) the content and format for the collection and reporting of data referred to in paragraph 4;

(c) the practical arrangements for the exchange of knowledge between holders of a hospital exemption approval within the same Member State or in different Member States;

(d) modalities for the preparation and use of ATMPs under hospital exemption on a non-routine basis.

Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 217(2).

8. By … [five years from the date of entry into force of this Directive] and every five years thereafter, the Agency shall submit a report to the Commission on the experience acquired with hospital exemption approvals. The reports shall be prepared on the basis of contributions from Member States and the data referred to in paragraph 4. The reports shall be made publicly available.

Article 4

Exemptions under certain circumstances

1. A Member State may, in order to meet special needs, exempt from the requirements of this Directive medicinal products supplied in response to a bona fide unsolicited order or anticipated bona fide unsolicited order, formulated or used in accordance with the specifications of an authorised healthcare professional and intended to meet the special needs of individual patients under the direct personal responsibility of that authorised healthcare professional. However, in such cases, the Member State shall encourage healthcare professionals and patients to report data on the safety of the use of such medicinal products to the competent authority of that Member State in accordance with Article 100.

   For allergen medicinal products supplied in accordance with this paragraph, the competent authority of the Member State may request the submission of relevant information in accordance with Annex II.

2. In duly justified cases, where a Member State considers other measures are insufficient to ensure the availability of specific medicinal products or suitable alternatives for patients in that Member State, it may temporarily allow the preparation and supply of medicinal products to:

   (a) mitigate or resolve a shortage in that Member State;

(b) address the specific needs of patients in that Member State in a situation where a marketing authorisation for a medicinal product has been withdrawn at the request of the marketing authorisation holder for reasons unrelated to the quality, safety or efficacy of the medicinal product; or

(c) address the specific needs of patients in that Member State in a situation where there is an authorised medicinal product in the Union but it does not have the specific strength, pharmaceutical form or formulation needed to address those needs.

The exemptions referred to in this paragraph shall apply only to the extent necessary to meet the specific needs of patients in the Member State concerned and only where:

(a) there is no suitable alternative medicinal product authorised in the Union; or

(b) such an alternative exists, but is not available within that Member State or cannot be supplied in accordance with paragraph 1 of this Article.

In addition, for the purposes of the first subparagraph, point (a), the exemption shall apply only if the shortage in that Member State cannot be resolved through Union coordinated actions.

The Member State shall endeavour, to the extent possible, to address the shortage referred to in the first subparagraph, point (a), by applying this Directive and Regulation (EU) 2026/…[+], before having recourse to this paragraph. Purely financial considerations shall not constitute specific needs to justify the application of this paragraph.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

For medicinal products prepared and supplied in accordance with this paragraph, the Member State shall ensure that:

(a) the preparation of the medicinal product is approved by the competent authority of that Member State on the basis of an assessment of the case and on public health grounds;

(b) in the case of a shortage referred to in the first subparagraph, point (a), the approval under point (a) of this subparagraph is revoked when the shortage is resolved or the medicinal product can be supplied in accordance with paragraph 1;

(c) in the cases other than shortages, referred to in the first subparagraph, points (b) and (c), the approval under point (a) of this subparagraph is limited in time, the necessity for the exemption is assessed at appropriate intervals and the approval is revoked without undue delay when a suitable medicinal product is authorised in the Union and available within that Member State or if the medicinal product can be supplied in accordance with paragraph 1;

(d) appropriate oversight by the competent authority of that Member State is in place and in particular any issues with regard to the quality and safety of the medicinal product are monitored and evaluated;

(e) the facility preparing the medicinal product complies with the principles of good manufacturing practice referred to in Article 163;

(f) the quality, safety and efficacy and the favourable benefit-risk balance of the medicinal product is confirmed by the competent authority of that Member State;

(g) the medicinal product is supplied to patients under the supervision of an authorised healthcare professional.

3. Member States may temporarily exempt from the requirements of this Directive medicinal products manufactured and supplied exclusively to the armed forces for military or defence purposes and prepared under the responsibility of the national authority for military or defence matters on the basis of national monographs for the manufacture and quality assessment of those medicinal products.

4. Without prejudice to Article 30 of Regulation (EU) 2026/…[+], Member States may temporarily authorise the use and distribution of an unauthorised medicinal product in response to a suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.

5. Member States shall ensure that, irrespective of whether a national marketing authorisation or a centralised marketing authorisation has been granted, marketing authorisation holders, manufacturers and healthcare professionals are not subject to civil or administrative liability for any consequences resulting from the use of a medicinal product otherwise than for the authorised therapeutic indications or from the use of an unauthorised medicinal product, where such use is recommended or required by a competent authority of a Member State in response to a suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

6. Liability for defective products, as provided for by Directive (EU) 2024/2853 of the European Parliament and of the Council[46], shall not be affected by paragraph 5 of this Article.

Article 5

Definitions

1. For the purposes of this Directive, the following definitions apply:

(1) 'medicinal product' or 'medicinal product for human use' means:

(a) any substance or combination of substances that is presented as having properties for treating or preventing disease in human beings; or

(b) any substance or combination of substances that may be used in or administered to human beings with a view to either restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis;

(2) 'substance' means any matter irrespective of origin which may be:

(a) human, such as human tissues and cells, human blood, human secretions and human blood products;

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[46] Directive (EU) 2024/2853 of the European Parliament and of the Council of 23 October 2024 on liability for defective products and repealing Council Directive 85/374/EEC (OJ L, 2024/2853, 18.11.2024, ELI: http://data.europa.eu/eli/dir/2024/2853/oj).

(b) animal, such as whole animals, animal organs and parts thereof, animal tissues and cells, animal secretions, toxins, extracts, animal blood and animal blood products;

(c) vegetal, such as plants, including algae, parts of plants, plant secretions and exudates, and extracts;

(d) chemical, such as chemical elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis;

(e) micro-organisms, such as bacteria, viruses and protozoa;

(f) fungi, such as micro-fungi (yeast);

(3) 'active substance' means any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to making a medical diagnosis;

(4) 'starting material' means any material from which an active substance is manufactured or extracted;

(5) 'intermediate product' means any partly processed material which must undergo further manufacturing steps before it becomes a bulk medicinal product or finished medicinal product;

(6) ‘excipient’ means any ingredient of a medicinal product other than the active substance;

(7) ‘functional excipient’ means an excipient that contributes to or enhances the performance of a medicinal product or performs an action that is ancillary to that of the active substance but does not make any therapeutic contribution of its own;

(8) ‘advanced therapy medicinal product’ or ‘ATMP’ means an advanced therapy medicinal product as defined in Article 2(1), point (a), of Regulation (EC) No 1394/2007;

(9) ‘combined advanced therapy medicinal product’ or ‘combined ATMP’ means a combined advanced therapy medicinal product as defined in Article 2(1), point (d), of Regulation (EC) No 1394/2007, including where a gene therapy medicinal product is part of the combined advanced therapy medicinal product;

(10) ‘allergen medicinal product’ means any medicinal product that is intended to identify or induce a specific acquired alteration in the immunological response to an allergen;

(11) ‘non-clinical’, as regards a study or test, means a study or a test that is conducted *in vitro*, *ex vivo*, *in silico* or *in chemico*, or a non-human *in vivo* test related to the investigation of the safety and efficacy of a medicinal product, such as simple and complex human cell-based assays, microphysiological systems including organ-on-chip, computer modelling and other *in silico* methods, other non-human or human biology-based test methods and animal-based tests;

(12) ‘reference medicinal product’ means a medicinal product that is or has been authorised by a Member State or by the Commission under Article 6, in accordance with Article 7;

(13) ‘generic medicinal product’ means a medicinal product that has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product;

(14) ‘biological medicinal product’ means a medicinal product, the active substance of which is produced by or extracted from a biological source and which, due to its complexity, its characterisation and the determination of its quality, may require a combination of physico-chemical-biological testing, together with its control strategy;

(15) ‘biosimilar medicinal product’ means a biological medicinal product that is similar to a reference biological medicinal product and has the same strength, pharmaceutical form and route of administration;

(16) ‘letter of access’ means an original document, signed by the owner of the data or the owner’s representative, giving permission to the competent authority of the Member State or the Agency, as applicable, or to the Commission to use the data for the benefit of a third party for the purpose of this Directive;

(17) ‘fixed-dose combination medicinal product’ means a medicinal product consisting of a combination of active substances intended to be placed on the market as a single pharmaceutical form;

(18) ‘multi-medicinal product package’ means a package that contains more than one medicinal product under a single invented name and intended to be used in a medical treatment where the individual medicinal products in the package are administered simultaneously or sequentially for medical purposes;

(19) ‘radiopharmaceutical’ means any medicinal product that, when ready for use, contains one or more radionuclides (radioactive isotopes) included for a medicinal purpose;

(20) ‘radionuclide generator’ means any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which is to be obtained by elution or by any other method and used in a radiopharmaceutical;

(21) ‘kit for radiopharmaceutical preparation’ means any preparation to be reconstituted or combined with radionuclides in the final radiopharmaceutical, usually prior to its administration;

(22) ‘radionuclide precursor’ means any radionuclide produced for the radio-labelling of another substance prior to administration;

(23) ‘antimicrobial’ means any medicinal product with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and antiprotozoals;

(24) ‘antimicrobial resistance’ means the ability of a micro-organism to survive or to grow in the presence of a concentration of an antimicrobial agent that is usually or was previously sufficient to inhibit the growth of or to kill that micro-organism;

(25) ‘integral combination of a medicinal product with a medical device’ means a combination of a medicinal product with a medical device and where:

(a) the two form an integral product and the action of the medicinal product is principal and not ancillary to that of the medical device; or

(b) the medicinal product is intended to be administered by the medical device and the two are placed on the market in such a way that they form a single integral product that is intended exclusively for use in the given combination and where the medical device is not reusable;

(26) ‘medicinal product in exclusive use with a medical device or with an *in vitro* diagnostic medical device’ means a medicinal product presented in a package with a medical device or intended for use with a specific medical device or with an *in vitro* diagnostic medical device, and referenced in the summary of product characteristics;

(27) ‘combination of a medicinal product with a product other than a medical device’ means a specific combination of a medicinal product with a product other than a medical device or than an *in vitro* diagnostic medical device, intended for use in that combination in accordance with the summary of product characteristics;

(28) ‘medical device’ means a medical device as defined in Article 2, point (1), of Regulation (EU) 2017/745;

(29) ‘*in vitro* diagnostic medical device’ means an *in vitro* diagnostic medical device as defined in Article 2, point (2), of Regulation (EU) 2017/746;

(30) ‘immunological medicinal product’ means:

(a) a vaccine, allergen medicinal product or other medicinal product eliciting an active and specific immune response;

(b) a medicinal product consisting of toxins, serums, polyclonal or monoclonal antibodies or other immunoglobulins and used to produce passive immunity or to diagnose the state of immunity;

(31) ‘vaccine’ means a medicinal product that is intended to elicit an immune response for the prevention, including post-exposure prophylaxis, and treatment of diseases caused by an infectious agent;

(32) ‘gene therapy medicinal product’ means a medicinal product, other than a vaccine against infectious diseases, that contains or consists of:

(a) a substance or combination of substances intended to edit the host genome in a sequence-specific manner or that contains or consists of cells that have been subjected to such modification; or

(b) a recombinant or synthetic nucleic acid used in or administered to human beings with a view to regulating, replacing or adding a genetic sequence that mediates its effect by the long-lasting transcription or translation of the transferred genetic materials, or that contains or consists of cells that have been subjected to such modifications;

(33) ‘somatic cell therapy medicinal product’ means a biological medicinal product that has the following characteristics:

(a) contains or consists of cells or tissues that have been subjected to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;

(b) is presented as having properties for, or is used in or administered to, human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.

(34) 'platform technology' means a technology or collection of technologies that has the potential to be incorporated in, or used by, more than one medicinal product, that is comprehensive, well-characterised, reproducible and standardised, that is used for the development, the manufacturing process or quality control of medicinal products, that relies on prior knowledge and that is established in accordance with scientific principles for which there is reasonable scientific certainty that they will remain unchanged across medicinal products;

(35) 'platform technology master file' means a document, prepared by the owner of the platform technology, that contains a detailed description of the platform technology;

(36) 'SoHO-derived medicinal product other than ATMPs' means any medicinal product containing, consisting of or deriving from a substance of human origin, other than tissues and cells, that is of standardised consistency and is prepared by:

(a) a method involving an industrial process which includes pooling of donations; or

(b) a process that extracts an active ingredient from the substance of human origin or transforms the substance of human origin by changing its inherent properties;

(37) ‘substance of human origin’ or ‘SoHO’ means a substance of human origin as defined in Article 3, point (1), of Regulation (EU) 2024/1938;

(38) ‘risk management plan’ means a detailed description of the risk management system;

(39) ‘risk management system’ means a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those activities and interventions;

(40) ‘environmental risk assessment’ or ‘ERA’ means the evaluation of the risks to the environment or risks to public health, posed by the release of the medicinal product into the environment following the use and disposal of the medicinal product, and the identification of risk prevention, limitation and mitigation measures, and for antimicrobials, an evaluation also of the risk for antimicrobial resistance selection in the environment due to the manufacture, use and disposal of that medicinal product;

(41) ‘risks related to use of the medicinal product’ means any risk:

(a) relating to the quality, safety or efficacy of the medicinal product as regards patients’ health or public health;

(b) of undesirable effects on the environment posed by the medicinal product;

(c) of undesirable effects on public health due to the release of the medicinal product into the environment, including antimicrobial resistance;

(42) ‘active substance master file’ means documentation prepared by the manufacturer of the active substance that contains particulars and documents on the quality of an active substance, including a detailed description of the manufacturing process, quality control during manufacture and process validation;

(43) ‘paediatric investigation plan’ means a research and development programme aimed at ensuring that the necessary data are generated to determine the conditions under which a medicinal product may be authorised to treat the paediatric population;

(44) ‘paediatric population’ means that part of the population from birth up to 18 years of age;

(45) ‘medical prescription’ means any medicinal prescription that is issued by a professional person qualified to do so;

(46) ‘abuse of medicinal products’ means the intentional excessive use of medicinal products, whether persistent or sporadic, that is accompanied by harmful physical or psychological effects;

(47) ‘benefit-risk balance’ means an evaluation of the positive therapeutic effects of a medicinal product in relation to the risks referred to in point (41)(a);

(48) ‘marketing authorisation holder representative’ means the person, commonly known as the local representative, designated by the marketing authorisation holder to represent the marketing authorisation holder in the Member State concerned;

(49) ‘package leaflet’ means a leaflet containing information that is intended for the user and that accompanies the medicinal product;

(50) ‘outer packaging’ means the packaging into which the immediate packaging is placed;

(51) ‘immediate packaging’ means the container or other form of packaging that is in direct contact with the medicinal product;

(52) ‘labelling’ means information on the immediate packaging or on the outer packaging;

(53) ‘name of the medicinal product’ means:

(a) an invented name, that is not liable to be confused with the common name, or

(b) a common name or scientific name accompanied by a trademark or by the name of the marketing authorisation holder;

(54) ‘common name’ means the international non-proprietary name recommended by the World Health Organization for an active substance;

(55) ‘strength’, as regards a medicinal product, means the content of the active substances in a medicinal product, expressed quantitatively per dosage unit, per unit of volume or per unit of weight according to the dosage form;

(56) ‘falsified medicinal product’ means any medicinal product with a false representation of:

(a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients or the strength of those ingredients;

(b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or

(c) its history, including the records and documents relating to the distribution channels used;

This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights.

(57) ‘public health emergency’ means a public health emergency recognised at Union level by the Commission under Article 23(1) of Regulation (EU) 2022/2371;

(58) ‘not-for-profit entity’ means a natural or legal person that does not make or intend to make profits or that is not controlled directly or indirectly by any entity that is profit-making, and that has not concluded any agreement with such an entity concerning sponsorship of or participation in the development of the medicinal product and in the case of a legal person, that is not owned by such an entity; ‘entities not engaged in an economic activity’ referred to in Annex V to Regulation (EU) 2024/568 of the European Parliament and of the Council[47] shall be considered to be not-for-profit entities;

(59) ‘micro, small and medium-sized enterprises’ means micro, small and medium-sized enterprises as defined in Article 2 of the Annex to Commission Recommendation 2003/361/EC[48];

(60) ‘variation’ or ‘variation of the terms of a marketing authorisation’ means:

(a) any amendment to the contents of the particulars and documents referred to in Article 7(2), Articles 10 to 15 or Article 65 of this Directive, in Annexes I and II thereto and in Article 7 of Regulation (EU) 2026/…[+]; or

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47 Regulation (EU) 2024/568 of the European Parliament and of the Council of 7 February 2024 on fees and charges payable to the European Medicines Agency, amending Regulations (EU) 2017/745 and (EU) 2022/123 of the European Parliament and of the Council and repealing Regulation (EU) No 658/2014 of the European Parliament and of the Council and Council Regulation (EC) No 297/95 (OJ L, 2024/568, 14.2.2024, ELI: http://data.europa.eu/eli/reg/2024/568/oj).

48 Commission Recommendation 2003/361/EC of 6 May 2003 concerning the definition of micro, small and medium-sized enterprises (OJ L 124, 20.5.2003, p. 36, ELI: http://data.europa.eu/eli/reco/2003/361/oj).

+ OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(b) any amendment to the terms of the decision granting the marketing authorisation for a medicinal product, including the summary of product characteristics and any conditions, obligations or restrictions affecting the marketing authorisation, or changes to the labelling or the package leaflet related to changes to the summary of product characteristics;

(61) ‘post-authorisation safety study’ means any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures;

(62) ‘pharmacovigilance system’ means a system used by the marketing authorisation holder or by Member States to fulfil the tasks and responsibilities set out in Chapter IX and designed to monitor the safety of authorised medicinal products and detect any change to their benefit-risk balance;

(63) ‘pharmacovigilance system master file’ means a detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised medicinal products;

(64) ‘adverse reaction’ means a response to a medicinal product that is noxious and unintended;

(65) ‘serious adverse reaction’ means an adverse reaction that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or a birth defect;

(66) ‘unexpected adverse reaction’ means an adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics;

(67) ‘homeopathic medicinal product’ means a medicinal product prepared from homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States;

(68) ‘traditional herbal medicinal product’ means a herbal medicinal product that fulfils the conditions laid down in Article 138(1);

(69) ‘herbal medicinal product’ means any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more herbal preparations;

(70) ‘herbal substances’ means all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried or fresh form, and certain exudates that have not been subjected to a specific treatment; they are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author);

(71) ‘herbal preparations’ means preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation, including comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates;

(72) ‘corresponding product’ means a product with the same active substances, irrespective of the excipients used, the same or similar intended purpose, equivalent strength and posology and the same or similar route of administration as the traditional herbal medicinal product in respect of which a traditional-use registration has been applied for;

(73) ‘manufacture of medicinal products’ means any operation involved in producing a medicinal product from active substances and excipients, and any related operation, including processing, filling, sterilisation and assembly, labelling, immediate packaging and outer packaging operations, and repackaging, storage, quality control testing and release;

(74) ‘decentralised manufacturing’ means a set of manufacturing activities related to medicinal products that are carried out under the control of a central site which supervises one or more decentralised sites where manufacturing activities take place and that are located in sufficient proximity to patients;

(75) ‘manufacture of active substances’ means any operation involved in producing an active substance from starting materials and any related operation, including processing, packaging and labelling operations, and repackaging, storage, quality control testing and release;

(76) ‘wholesale distribution’, as regards medicinal products, means all activities consisting of procuring, holding, supplying or exporting medicinal products, whether for profit or not, apart from supplying medicinal products to the public; such activities are carried out with manufacturers or their depositories, importers, other wholesale distributors or with pharmacists and other persons authorised or entitled to supply medicinal products to the public in the Member State concerned;

(77) ‘brokering of medicinal products’ means all activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person;

(78) ‘public service obligation’ means an obligation to ensure on a permanent basis an adequate range of medicinal products to meet the requirements of a specific geographical area and to deliver the supplies requested within a very short time over the whole of the area in question.

2. The Commission is empowered to adopt delegated acts in accordance with Article 218 to amend the definitions in paragraph 1, points (2) to (7), (9), (10), (14), (17) to (23), (25), (26), (27) and (30) to (36), to take account of technical and scientific progress and taking into account definitions agreed at Union and international level without amending the scope of the definitions.

Chapter II
Application requirements for national and centralised marketing authorisations

SECTION 1
GENERAL PROVISIONS

Article 6

Marketing authorisations

1. A medicinal product shall be placed on the market of a Member State only where a marketing authorisation has been granted in accordance with Chapter III of this Directive ('national marketing authorisation') or in accordance with Regulation (EU) 2026/…[+] ('centralised marketing authorisation').

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

2. Where an initial marketing authorisation has been granted for a medicinal product, any development of that medicinal product, such as additional therapeutic indications, strengths, pharmaceutical forms, administration routes, presentations, as well as any variations of the marketing authorisation, shall be included in the initial marketing authorisation or covered by a separate marketing authorisation as referred to in paragraph 1. All those marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of marketing authorisation applications under Articles 10 to 13, including as regards the expiry of the regulatory data protection period for applications using a reference medicinal product.

Article 7

General requirements for marketing authorisation applications

1. In order to obtain a marketing authorisation, an electronic marketing authorisation application shall be submitted to the competent authority of the Member State or the Agency, as applicable, in a common format. The Agency shall make the common format available after consultation with the Member States.

2. The marketing authorisation application shall include the particulars and documents listed in Annex I in accordance with Annex II. Where appropriate, the marketing authorisation application may include summary documents, certificates, protocols or master files in accordance with section 4 of this Chapter and with Annex II.

3. The documents and information concerning the results of the pharmaceutical and non-clinical tests and the clinical studies referred to in Annex I shall be accompanied by detailed summaries in accordance with Article 8 of this Directive and supportive raw data in accordance with Article 32(1), point (e), of this Directive or Article 7 of Regulation (EU) 2026/…[+].

4. The risk management system referred to in Annex I shall be proportionate to the identified risks and the potential risks of the medicinal product, and to the need for post-authorisation safety data.

5. The marketing authorisation application for a medicinal product that is not authorised in the Union at the time of entry into force of this Directive and for new therapeutic indications, including paediatric indications, new pharmaceutical forms, new strengths and new routes of administration of authorised medicinal products which are protected either by a supplementary protection certificate under Regulation (EC) No 469/2009, or by a patent which qualifies for the granting of a supplementary protection certificate, shall include one of the following:

   (a) the results of all studies conducted and details of all information collected in compliance with an agreed paediatric investigation plan;

   (b) a decision of the Agency granting a class or product-specific waiver pursuant to Article 77 of Regulation (EU) 2026/…[+];

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(c) a decision of the Agency granting a deferral pursuant to Article 83 of Regulation (EU) 2026/…[+];

(d) a decision of the Agency taken in consultation with the Commission pursuant to Article 85 of Regulation (EU) 2026/…[+] to temporarily derogate from the provisions referred to in points (a) to (c) of this subparagraph in the case of public health emergencies.

The documents under the first subparagraph, points (a) to (d), shall, cumulatively, cover all subsets of the paediatric population.

6. Paragraph 5 of this Article shall not apply to medicinal products authorised under Articles 10, 12, 14 and 129 to 145 and medicinal products authorised under Articles 11 and 13 which are not protected either by a supplementary protection certificate under Regulation (EC) No 469/2009, or by a patent which qualifies for the granting of a supplementary protection certificate.

7. The marketing authorisation applicant shall demonstrate that the principle of replacement, reduction and refinement of animal testing for scientific purposes has been applied in accordance with Directive 2010/63/EU with regard to any animal study conducted in support of the application.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

The marketing authorisation applicant shall not carry out animal testing in the case where scientifically satisfactory non-animal testing methods are available. Where scientifically satisfactory non-animal testing methods are not available, animal testing shall be carried out in accordance with Directive 2010/63/EU.

Article 8

Expert verification

1. The marketing authorisation applicant shall ensure that the detailed summaries referred to in Article 7(3) have been drawn up and signed by experts with the necessary technical or professional qualifications before they are submitted to the competent authorities of the Member State or the Agency, as applicable. The technical or professional qualifications of the experts shall be set out in a brief curriculum vitae.

2. The experts referred to in paragraph 1 of this Article shall justify any use made of scientific literature under Article 14 in accordance with the requirements set out in Annex II.

Article 9

Medicinal products manufactured outside the Union

Member States shall take all appropriate measures to ensure that:

(a) their competent authorities or the Agency, as applicable, verify that manufacturers and importers of medicinal products coming from third countries are able to carry out the manufacture of medicinal products in compliance with the particulars supplied pursuant to Annex I and carry out controls according to the methods described in the particulars accompanying the application in accordance with Annex I;

(b) their competent authorities or the Agency, as applicable, may allow manufacturers and importers of medicinal products coming from third countries, in justifiable cases, to have certain stages of manufacture or certain of the controls referred to in point (a) carried out by third parties; in such cases, the verifications by the competent authorities shall also be made in the establishment designated.

SECTION 2

SPECIFIC REQUIREMENTS FOR ABRIDGED, BIBLIOGRAPHIC OR CONSENT BASED MARKETING AUTHORISATION APPLICATIONS

Article 10

Marketing authorisation applications concerning generic medicinal products

1. By way of derogation from Article 7(2), the applicant for a marketing authorisation for a generic medicinal product shall not be required to provide to the competent authorities of the Member States or the Agency, as applicable, the results of non-clinical tests and of clinical studies if equivalence of the generic medicinal product with the reference medicinal product is demonstrated.

2. For the purpose of demonstrating the equivalence of a generic medicinal product as referred to in paragraph 1, the marketing authorisation applicant shall:

   (a) submit equivalence studies to the competent authorities of the Member States or the Agency, as applicable, or provide a justification as to why such studies were not performed, and

   (b) demonstrate that the generic medicinal product meets the relevant criteria set out in the relevant detailed guidelines.

3. Paragraph 1 shall also apply if the reference medicinal product has not been authorised in the Member State in which the marketing authorisation application for the generic medicinal product is submitted. In this case, the marketing authorisation applicant shall indicate in the marketing authorisation application for the generic medicinal product the name of the Member State in which the reference medicinal product is or has been authorised.

At the request of the competent authority of the Member State in which the marketing authorisation application for the generic medicinal product is submitted, the competent authority of the other Member State shall transmit within a period of one month a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference medicinal product and, if necessary, any other relevant documentation.

The various immediate-release oral pharmaceutical forms shall be considered to be the same pharmaceutical form.

4. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety or efficacy. The marketing authorisation applicant for the generic medicinal product shall submit additional information to demonstrate that the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance do not differ significantly in respect of those properties.

5. Where there is a significant difference in properties as referred to in paragraph 4, the applicant shall submit additional information in order to demonstrate the safety or efficacy of the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the authorised active substance of the reference medicinal product in a marketing authorisation application under Article 11.

Article 11

Marketing authorisation applications for hybrid medicinal products

In the case of a marketing authorisation application for a medicinal product which does not fall within the definition of a generic medicinal product or differs in strength, pharmaceutical form, route of administration or therapeutic indications compared to the reference medicinal product ('hybrid medicinal product'), the results of the relevant non-clinical tests or clinical studies shall be provided to the competent authorities of the Member States or the Agency, as applicable, to the extent necessary to establish a scientific bridge to the data relied upon in the marketing authorisation for the reference medicinal product, and to demonstrate the safety and efficacy profile of the hybrid medicinal product.

Article 12

Marketing authorisation applications for biosimilar medicinal products

For a biosimilar medicinal product, the results of appropriate comparability tests and studies shall be provided to the competent authorities of the Member States or the Agency, as applicable. The type and quantity of supplementary data to be provided shall comply with the relevant criteria set out in Annex II and the related detailed guidelines. The results of other tests and studies from the reference medicinal product's dossier shall not be required.

Article 13

Marketing authorisation applications for bio-hybrid medicinal products

In cases where the biological medicinal product does not fall within the definition of a biosimilar medicinal product or differs in strength, pharmaceutical form, route of administration or therapeutic indications compared to the reference biological medicinal product ('bio-hybrid medicinal product'), the results of the appropriate non-clinical tests or clinical studies shall be provided to the competent authorities of the Member States or the Agency, as applicable, to the extent necessary to establish a scientific bridge to the data relied upon in the marketing authorisation for the reference biological medicinal product, and to demonstrate the safety and efficacy profile of the bio-hybrid medicinal product.

Article 14

Marketing authorisation applications based on bibliographic data

The marketing authorisation applicant shall, by way of derogation from Article 7(2), not be required to provide the results of non-clinical tests or clinical studies if the marketing authorisation applicant can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Union for the same therapeutic use and route of administration for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex II. In such cases, the test and trial results shall be replaced by appropriate bibliographic data in the form of scientific literature, and the marketing authorisation applicant shall establish a scientific bridge between the bibliographic data and the medicinal product concerned.

Marketing authorisation applications based on this Article shall only be submitted provided that the marketing authorisation applicant demonstrates that:

(a) at the time of submission of the marketing authorisation application, no reference medicinal product is or has been authorised in the Union for the active substance of the medicinal product concerned;

(b) while a reference medicinal product has been authorised in the Union for the active substance of the medicinal product concerned, it is not available on the market within the Union at the time of submission of the marketing authorisation application; or

(c) the marketing authorisation application concerns a herbal medicinal product for which efficacy and safety have been established and documented in a relevant Union herbal monograph.

Article 15

Marketing authorisation applications based on consent

Following the granting of a marketing authorisation, the marketing authorisation holder may, by letter of access, allow use to be made of all documentation referred to in Article 7(2) for the purpose of examining marketing authorisation applications relating to other medicinal products with the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

SECTION 3

SPECIFIC REQUIREMENTS FOR MARKETING AUTHORISATION APPLICATIONS FOR CERTAIN CATEGORIES OF MEDICINAL PRODUCTS

Article 16

Fixed-dose combination medicinal products, platform marketing authorisation and multi-medicinal product packages

1. Where duly justified for clinical purposes, a marketing authorisation may be granted for a fixed-dose combination medicinal product.

2. Where duly justified for clinical purposes, a marketing authorisation may be granted for a medicinal product comprised of a fixed component and a variable component that is pre-defined in order to, where appropriate, target different variants of an infectious agent or, where necessary, to tailor the medicinal product to characteristics of an individual patient or a group of patients (‘platform marketing authorisation’).

Before submitting a marketing authorisation application for such a medicinal product, the applicant shall obtain the agreement of the competent authority of the Member State or the Agency, as applicable, for the submission of the application.

3. Where justified for public health reasons, a marketing authorisation may be granted, in exceptional circumstances, for a multi-medicinal product package where the active substances cannot be combined within a fixed- dose combination medicinal product.

Before submitting a marketing authorisation application for such a multi-medicinal product package, the applicant shall obtain the agreement of the competent authority of the Member State or the Agency, as applicable, for the submission of the application.

Article 17

Radiopharmaceuticals

1. A marketing authorisation shall be required for radionuclide generators, kits for radiopharmaceutical preparations, and radionuclide precursors, unless they are used as starting materials, active substances or intermediates of radiopharmaceuticals covered by a marketing authorisation under Article 6(1).

2. A marketing authorisation shall not be required for a radiopharmaceutical that is prepared at the time of use by a person or by an establishment that is authorised, in accordance with national legislation, to use such radiopharmaceutical in an approved healthcare establishment, and that is prepared exclusively from authorised radionuclide generators, kits for radiopharmaceutical preparations or radionuclide precursors in accordance with the summary of product characteristics.

Article 18

Antimicrobials

1. Where the marketing authorisation application concerns an antimicrobial, the application shall, in addition to the information referred to in Article 7(2), contain the following in accordance with Annex I:

   (a) an antimicrobial stewardship plan;

   (b) a description of the special information requirements outlined in Article 72.

2. The competent authority of the Member State or the Agency, as applicable, shall review the information submitted in accordance with paragraph 1. The competent authority of the Member State or the Agency, as applicable, shall impose obligations on the marketing authorisation holder if it finds the risk mitigation measures contained in the antimicrobial stewardship plan to be unsatisfactory.

3. Where a pack of antimicrobials is intended for direct dispensing to patients, the marketing authorisation holder shall ensure that the pack size of the antimicrobials corresponds to the usual posology and duration of treatment.

Article 19

Integral combinations of a medicinal product with a medical device

1. For integral combinations of a medicinal product with a medical device, the marketing authorisation applicant shall submit data demonstrating the safe and effective use of the integral combination of the medicinal product with the medical device.

   The competent authority of the Member State or the Agency, as applicable, shall assess the benefit-risk balance of the integral combination of a medicinal product with a medical device, taking into account the suitability of the use of the medicinal product together with the medical device.

2. The relevant general safety and performance requirements set out in Annex I to Regulation (EU) 2017/745 shall apply as far as the safety and performance of the medical device that is part of the integral combination of a medicinal product with a medical device are concerned.

3. The marketing authorisation application for the integral combination of a medicinal product with a medical device shall include documentation in accordance with Annex II to this Directive, demonstrating the conformity of the medical device that is part of the integral combination of a medicinal product with a medical device with the general safety and performance requirements set out in Annex I to Regulation (EU) 2017/745 (‘conformity assessment’), including the results of the conformity assessment or, where relevant, an opinion on the conformity of that medical device with the general safety and performance requirements set out in Annex I to Regulation (EU) 2017/745 by a notified body.

4. In its assessment of the integral combination of a medicinal product with a medical device, the competent authority of the Member State or the Agency, as applicable, shall recognise the results of the conformity assessment, including, where relevant, the results of the assessment by a notified body.

5. The marketing authorisation applicant shall, upon request from the competent authority of the Member State or the Agency, as applicable, submit any additional information related to the medical device and that is relevant for the benefit-risk balance assessment of the integral combination of a medicinal product with a medical device.

Article 20

Medicinal products in exclusive use with a medical device or with an in vitro diagnostic medical device

1. For medicinal products in exclusive use with a medical device or with an *in vitro* diagnostic medical device, the marketing authorisation applicant shall submit data demonstrating the safe and effective use of the medicinal product taking into account its use with the medical device or with the *in vitro* diagnostic medical device.

   The competent authorities of the Member States or the Agency, as applicable, shall assess the benefit-risk balance of the medicinal product taking into account the use of the medicinal product together with the medical device or *in vitro* diagnostic medical device.

2. For medicinal products in exclusive use with a medical device or with an *in vitro* diagnostic medical device, the medical device or *in vitro* diagnostic medical device shall meet the requirements set out in Regulation (EU) 2017/745 or (EU) 2017/746, as applicable.

3. The marketing authorisation application for a medicinal product in exclusive use with a medical device or with an *in vitro* diagnostic medical device shall include documentation in accordance with Annex II demonstrating the conformity of the medical device or *in vitro* diagnostic medical device with the general safety and performance requirements including, where relevant, the results of the assessment or the conformity assessment report by a notified body.

4. In its assessment of the medicinal product in exclusive use with a medical device or with an *in vitro* diagnostic medical device, the competent authorities of the Member States or the Agency, as applicable, shall recognise the results of the assessment of the conformity of the medical device or in-vitro diagnostic medical device concerned with the general safety and performance requirements set out in Annex I to Regulation (EU) 2017/745 or Annex I to Regulation (EU) 2017/746, as applicable, including, where relevant, the results of the assessment by a notified body.

5. The marketing authorisation applicant shall, upon request from the competent authorities of the Member States or the Agency, as applicable, submit any additional information related to the medical device or *in vitro* diagnostic medical device and that is relevant for the benefit-risk balance assessment of the medicinal product in exclusive use with a medical device or with an *in vitro* diagnostic medical device, taking into account the use of the medicinal product with the medical device or *in vitro* diagnostic medical device.

6. If the action of the medicinal product is not ancillary to that of the medical device or *in vitro* diagnostic medical device, the medicinal product shall comply with the requirements of this Directive and of Regulation (EU) 2026/…[+], taking into account its use with the medical device or *in vitro* diagnostic medical device, without prejudice to the specific requirements of Regulation (EU) 2017/745 or (EU) 2017/746, as applicable.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

For the purposes of this paragraph, the marketing authorisation applicant shall, upon request from the competent authorities of the Member States or the Agency, as applicable, submit any additional information related to the medical device or *in vitro* diagnostic medical device, taking into account its use with the medicinal product, and that is relevant for the post-authorisation monitoring of the medicinal product, without prejudice to the specific requirements of Regulation (EU) 2026/…[+].

Article 21

Combinations of medicinal products with products other than medical devices

1. For combinations of a medicinal product with a product other than a medical device, the marketing authorisation applicant shall submit data demonstrating the safe and effective use of the combination of the medicinal product and the other product.

   The competent authority of the Member State or the Agency, as applicable, shall assess the benefit-risk balance of the combination of a medicinal product with a product other than a medical device, taking into account the use of the medicinal product together with the other product.

2. The marketing authorisation applicant shall, upon request from the competent authority of the Member State or the Agency, as applicable, submit any additional information related to the product other than a medical device and that is relevant for the benefit-risk balance assessment of the combination of a medicinal product with a product other than a medical device, taking into account the suitability of the use of the medicinal product with the other product.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

3. The competent authority of the Member State or the Agency, as applicable, may request an opinion from the authority responsible for the supervision of the product other than a medical device.

SECTION 4

SPECIFIC DOSSIER REQUIREMENTS

Article 22

Risk management plan

1. The applicant of a marketing authorisation for a medicinal product referred to in Articles 10 and 12 shall not be required to submit a risk management plan and a summary thereof, provided that no additional risk minimisation measures exist for the reference medicinal product and provided that the marketing authorisation for the reference medicinal product has not been withdrawn prior to the submission of the marketing authorisation application.

2. The risk management plan for medicinal products referred to in Articles 11 and 13 shall be limited to the differences between those medicinal products and the reference medicinal product, provided that no additional risk minimisation measures exist for the reference medicinal product and provided that the marketing authorisation for the reference medicinal product has not been withdrawn prior to the submission of the marketing authorisation application.

Article 23

ERA and other environmental information

1. When preparing the ERA to be submitted pursuant to Article 7(2), the marketing authorisation applicant shall take into account the scientific guidelines on the ERA for medicinal products for human use as referred to in paragraph 5 of this Article or provide duly justified reasons for any divergence from the scientific guidelines to the competent authority of the Member State or the Agency, as applicable, in a timely manner. Where available, the marketing authorisation applicant shall take into account existing risk assessments performed under other Union legal acts.

2. The ERA shall indicate whether the medicinal product or any of its ingredients or other constituents is an endocrine active agent or has been assigned to one of the following hazard classes in accordance with the criteria set out in Annex I to Regulation (EC) No 1272/2008 of the European Parliament and of the Council[49]:

   (a) persistent, bioaccumulative and toxic (PBT);

   (b) very persistent and very bioaccumulative (vPvB);

   (c) persistent, mobile and toxic (PMT);

   (d) very persistent and very mobile (vPvM).

[49] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (OJ L 353, 31.12.2008, p. 1, ELI: http://data.europa.eu/eli/reg/2008/1272/oj).

3. The applicant shall include in the ERA risk mitigation measures to avoid or, where it is not possible, limit emissions to air, water and soil of ingredients and constituents of medicinal products listed as pollutants in Directives 2000/60/EC, 2006/118/EC, 2008/105/EC and 2010/75/EU. The applicant shall provide a detailed explanation as to how the proposed risk mitigation measures are appropriate and sufficient to address the identified risks to the environment.

4. The ERA for antimicrobials shall include an evaluation of the risk for antimicrobial resistance selection in the environment due to the entire manufacturing supply chain inside and outside the Union, use and disposal, including by healthcare professionals and patients, of the antimicrobial taking into account, where relevant, the existing international standards that have established predicted no effect concentrations (PNECs) specific for antibiotics.

5. The Agency shall draw up scientific guidelines in accordance with Article 144(1), point (zm), of Regulation (EU) 2026/…[+], to specify technical details regarding the ERA requirements for medicinal products for human use, including for antimicrobials other than antibiotics. Where appropriate, the Agency shall consult the European Chemical Agency (ECHA), the European Food Safety Authority (EFSA), the European Environmental Agency (EEA) and the European Centre for Disease Prevention and Control (ECDC) on the drafting of these scientific guidelines.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

6. If new information pertaining to the assessment criteria of an ERA becomes available and could lead to a change to its conclusions, the marketing authorisation holder shall submit an updated ERA without undue delay to the competent authority of the Member State or the Agency, as applicable. The updated ERA shall include any relevant information from environmental monitoring, including monitoring under Directive 2000/60/EC, from eco-toxicity studies, from new or updated risk assessments under other Union legal acts, as referred to in paragraph 1 of this Article, and environmental exposure data.

   For an ERA conducted prior to … [24 months from the date of entry into force of this Directive], the competent authority of the Member State or the Agency, as applicable, shall request the marketing authorisation holder to update the ERA if information has been identified as missing concerning medicinal products that are potentially harmful to the environment.

7. For medicinal products referred to in Articles 10 to 13 and 15 and fixed-dose combination medicinal products, the marketing authorisation applicant may, when preparing the ERA, refer to ERA studies conducted for the reference medicinal product or to ERA studies for any other medicinal product containing the same active substances.

Article 24

ERA for medicinal products authorised before 30 October 2005

1. By … [30 months from the date of entry into force of this Directive], the Agency shall, after consultation with the competent authorities of the Member States, the ECHA, the EFSA, the EEA and the ECDC, establish a programme for those ERAs that are to be submitted in accordance with Article 23 for medicinal products that were authorised before 30 October 2005, that have not been the subject of an ERA, and that the Agency has identified as potentially harmful to the environment in accordance with paragraph 2 of this Article.

   The Agency shall make the programme publicly available.

2. The Agency shall establish the scientific criteria for the identification of medicinal products that are potentially harmful to the environment and for the prioritisation of ERAs for such products, using a risk-based approach. For those purposes, the Agency shall consult relevant stakeholders and may request marketing authorisation holders to submit relevant data or information.

3. The holder of a marketing authorisation for a medicinal product identified under the programme referred to in paragraph 1 shall submit an ERA for that medicinal product to the Agency. The outcome of the assessment of the ERA by the competent authority of the Member State or the Agency, as applicable, including a summary of the ERA data submitted by the marketing authorisation holder, shall be made publicly available by the Agency.

4. Where there are several medicinal products identified under the programme referred to in paragraph 1 that contain the same active substance and that are expected to pose the same risks to the environment, the competent authority of the Member State or the Agency, as applicable, shall encourage the marketing authorisation holders to conduct joint ERA studies for those medicinal products, to minimise unnecessary duplication of data and use of animals.

5. Where, for medicinal products referred to in Articles 10 to 13 and 15 and fixed-dose combination medicinal products, a joint ERA study, as referred to in paragraph 4 of this Article, has not been conducted and the reference medicinal product or the medicinal product containing the same active substance is included in the programme referred to in paragraph 1 of this Article, the ERA shall be submitted after the outcome of the assessment of the ERA for that reference medicinal product by the competent authority of the Member State or the Agency, as applicable, has been made publicly available by the Agency.

Article 25

ERA monograph system

1. The Agency shall, in collaboration with the competent authorities of the Member States, establish an active substance-based review system of ERA data for authorised medicinal products comprised of monographs for active substances (‘ERA monograph system’) and publish relevant information about that system. Each ERA monograph shall include a comprehensive set of physiochemical data, fate data and effect data based on an assessment of the active substance by the competent authority of the Member State or the Agency, as applicable.

2. The Agency shall select and prioritise active substances for which it shall prepare ERA monographs. That selection and prioritisation shall be based on risk-based criteria.

3. For the purpose of an ERA monograph, the Agency may request information, studies and data from competent authorities of the Member States and from marketing authorisation holders.

4. In cooperation with the competent authorities of the Member States, the Agency shall conduct a proof-of-concept pilot of ERA monographs to be completed by … [three years from the date of entry into force of this Directive].

5. The Commission is empowered to adopt delegated acts in accordance with Article 218 and based on the results of the proof-of-concept pilot referred to in paragraph 4 of this Article, to supplement this Directive by specifying the following:

(a) the content and format of ERA monographs;

(b) the procedures for adopting and updating the ERA monographs;

(c) the procedures for submission of information, studies and data referred to in paragraph 3;

(d) the risk-based criteria for the selection and prioritisation of active substances pursuant to paragraph 2;

(e) the use of ERA monographs in the context of new marketing authorisation applications for medicinal products to support the ERA for those medicinal products.

Article 26

Active substance master file

1. Marketing authorisation applicants may, instead of submitting the relevant data on a chemical active substance of a medicinal product required in accordance with Annex II, rely on an active substance master file, an active substance master file certificate granted by the Agency in accordance with this Article (‘active substance master file certificate’) or a certificate confirming that the quality of the active substance concerned is suitably controlled by the relevant monograph of the European Pharmacopoeia.

Marketing authorisation applicants shall only rely on an active substance master file if no certificate exists on the same active substance master file.

2. The Agency shall be responsible for granting active substance master file certificates.

3. The Agency may grant an active substance master file certificate to the manufacturer of an active substance in cases where the relevant data on the active substance concerned are not already covered by a monograph of the European Pharmacopoeia or by an active substance master file certificate.

In order to obtain an active substance master file certificate, an application for an active substance master file certificate shall be submitted to the Agency. The applicant for an active substance master file certificate shall demonstrate that the active substance concerned is not already covered by a monograph of the European Pharmacopoeia or an active substance master file certificate. The Agency shall examine the application for an active substance master file certificate and, in the case of a positive outcome, shall grant the active substance master file certificate, that shall be valid throughout the Union. The application for an active substance master file certificate may be submitted to the Agency separately from a marketing authorisation application. In the case of centralised marketing authorisations, the application for an active substance master file certificate may be submitted as part of the marketing authorisation application for the corresponding medicinal product.

The Agency shall set up and maintain a repository of active substance master files and corresponding assessment reports and certificates and ensure that personal data and information of a commercially confidential nature are protected. The Agency shall ensure that the competent authorities of the Member States have access to the repository.

4. The active substance master file and the active substance master file certificate shall cover all the information on the active substance required in accordance with Annex II.

5. The holder of an active substance master file certificate shall keep the active substance master file up to date in the light of scientific and technological progress and introduce the changes required to ensure that the active substance is manufactured and controlled in accordance with generally accepted scientific methods.

6. If requested by the Agency, the manufacturer of the active substance for which an application for an active substance master file certificate has been submitted or the holder of an active substance master file certificate shall undergo an inspection to verify the information contained in the application for an active substance master file certificate or in the active substance master file or their compliance with the principles of good manufacturing practice for active substances referred to in Article 163.

If the manufacturer of an active substance refuses to undergo such an inspection, the Agency may suspend or terminate the examination of the application for an active substance master file certificate.

7. If the holder of an active substance master file certificate does not fulfil the obligations set out in paragraphs 5 and 6, the Agency may suspend or withdraw the certificate and the competent authorities of the Member States or the Commission, as applicable, may suspend or revoke the marketing authorisation of a medicinal product relying on that certificate and take measures to prohibit the supply of that medicinal product.

8. The holder of a marketing authorisation for a medicinal product that has been granted on the basis of an active substance master file certificate remains responsible and liable for that medicinal product.

9. The Commission is empowered to adopt delegated acts in accordance with Article 218 to supplement this Directive by specifying the following:

   (a) the rules governing the content and format of the application for an active substance master file certificate;

   (b) the rules for the submission and examination of an application for an active substance master file certificate and for the granting of the certificate;

   (c) the rules for making active substance master file certificates publicly available;

   (d) the rules for introducing changes to the active substance master file and the active substance master file certificate;

   (e) the rules on access to the active substance master file and to the corresponding assessment report by competent authorities of the Member States;

(f) the rules on access to the active substance master file and to the corresponding assessment report by marketing authorisation applicants and marketing authorisation holders relying on an active substance master file certificate.

Article 27

Additional quality master files

1. Marketing authorisation applicants may, instead of submitting the relevant data on an active substance other than a chemical active substance, or on other substances present or used in the manufacture of a medicinal product, required in accordance with Annex II, rely on an additional quality master file, an additional quality master file certificate granted by the Agency in accordance with this Article ('additional quality master file certificate') or a certificate confirming that the quality of that substance is suitably controlled by the relevant monograph of the European Pharmacopoeia.

   Marketing authorisation applicants shall only rely on an additional quality master file certificate if no certificate exists on the same additional quality master file.

2. Article 26, paragraphs 1, 2, 4, 5, 7 and 8 shall also apply *mutatis mutandis* to additional quality master file certification.

3. The Commission is empowered to adopt delegated acts in accordance with Article 218 to supplement this Directive by identifying, in the light of scientific progress, the substances to which this Article shall apply. A substance shall only be identified under this paragraph if the use of additional quality master files is scientifically justified.

4. The Commission is empowered to adopt delegated acts in accordance with Article 218 to supplement this Directive by specifying:

(a) the rules governing the content and format of the application for an additional quality master file certificate;

(b) additional quality master files for which a certificate may be used in order to provide specific information on the quality of a substance present or used in the manufacture of a medicinal product;

(c) the rules for the examination of an application for an additional quality master file certificate;

(d) the rules for making the additional quality master file certificates publicly available;

(e) the rules for introducing changes to the additional quality master file and the additional quality master file certificate;

(f) the rules on access to the additional quality master file and the corresponding assessment report by the competent authorities of the Member States;

(g) the rules on access to the additional quality master file and to the corresponding assessment report by marketing authorisation applicants and marketing authorisation holders relying on an additional quality master file certificate.

5. If requested by the Agency, the manufacturer of a substance present or used in the manufacture of a medicinal product for which an application for an additional quality master file certificate has been submitted or the holder of an additional quality master file certificate shall undergo an inspection to verify the information contained in the application for the additional quality master file certificate or in the additional quality master file.

If the manufacturer of that substance refuses to undergo such an inspection, the Agency may suspend or terminate the examination of the application for the additional quality master file certificate.

Article 28

Platform technology master files

1. Marketing authorisation applicants may, instead of submitting the relevant data related to a platform technology required in accordance with Annex II, rely on a platform technology master file that is certified in accordance with paragraph 3 of this Article. The platform technology master file shall contain the information required in accordance with Annex II. The marketing authorisation applicants shall take into account the scientific guidelines published by the Agency in this regard.

2. Marketing authorisation holders relying on a certified platform technology master file shall keep the platform technology master file up to date in the light of scientific and technological progress and introduce the changes required to ensure that the platform technology is in accordance with generally accepted scientific methods and the state of the art. The holder of a marketing authorisation for a medicinal product who is relying on a certified platform technology master file shall remain responsible and liable for that medicinal product.

3. For a platform technology master file to be certified, an application for a certified platform technology master file shall be submitted to the Agency. The Agency shall examine the application and, in the event of a positive outcome, shall certify the platform technology master file.

4. The application for a certified platform technology master file can be submitted only after the Agency has confirmed the eligibility of the application for a certified platform technology master file. Once eligibility is confirmed, the application for a certified platform technology master file shall be submitted as part of the marketing authorisation application for the corresponding medicinal product or after the granting of the marketing authorisation for the corresponding medicinal product.

5. The Agency shall set up and maintain a repository of certified platform technology master files and corresponding assessments reports and ensure that personal data and information of a commercially confidential nature are protected. The Agency shall ensure that the competent authorities of the Member States have access to the repository.

6. If the owner of a certified platform technology master file does not fulfil the obligations set out in this Article, the Agency may suspend or withdraw the certification and the competent authorities of the Member States or the Commission, as applicable, may suspend or revoke the marketing authorisation of medicinal products relying on the certified platform technology master file and take measures to prohibit the supply of the medicinal products relying on that certified platform technology master file. The owner of a certified platform technology master file shall notify the marketing authorisation holders concerned without undue delay of any information that is relevant to fulfil their obligations in accordance with paragraph 2.

7. If requested by the Agency or, where relevant, the competent authority of a Member State, the platform technology shall be subject to an inspection to verify the information contained in the platform technology master file. If the applicant for a certified platform technology master file or the owner of the certified platform technology master file refuses to undergo such an inspection, the Agency may suspend or terminate the examination of the application for a certified platform technology master file or suspend or withdraw the certification.

Article 29

Decentralised manufacturing

1 Where justified by the specific properties of the manufactured medicinal product and considerations related to the quality, safety and efficacy of a medicinal product, such as short shelf life, or where proximity to the patient being treated or customisation for an individual patient is to the patient's benefit, the marketing authorisation applicant may request the competent authority of the Member State or the Agency, as applicable, to approve the use of decentralised manufacturing for the medicinal product concerned.

2. The request referred to in paragraph 1 shall be submitted as part of the marketing authorisation application in accordance with Annex II.

3. The competent authority of the Member State or the Agency, as applicable, shall assess the request referred to in paragraph 1 as part of the assessment of the marketing authorisation application.

4. The competent authority of the Member State or the Agency, as applicable, shall cooperate with all relevant regulatory authorities, including the competent authority of the Member State supervising the central site identified in the marketing authorisation application. The manufacturing authorisation of the central site granted under Article 146 shall be provided as part of the marketing authorisation procedure.

5. The approval to use decentralised manufacturing shall be included in the terms of the marketing authorisation.

6. The competent authority of the Member State or the Agency, as applicable, may withdraw an approval to use decentralised manufacturing where it concludes that the justification referred to in paragraph 1 is no longer valid or that the conditions for decentralised manufacturing as referred to in Articles 146 to 152 and Articles 155 to 157 are not complied with. The competent authority shall inform the competent authority of the Member State supervising the central site of such circumstances without undue delay.

7. The marketing authorisation holders making use of decentralised manufacturing shall provide the competent authority of the Member State or the Agency, as applicable, with any new information that might entail an amendment to the terms of the marketing authorisation as referred to in paragraph 5 of this Article, in accordance with Article 92.

8. The Commission may adopt implementing acts to set out the content and format of the request to use decentralised manufacturing and to specify the application of paragraph 1. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 217(2).

Article 30

Excipients

1. The applicant shall provide information on the excipients used in a medicinal product in accordance with the requirements set out in Annex II.

   The competent authority of the Member State or the Agency, as applicable, shall assess the excipients as part of the medicinal product.

2. Colours shall be used in medicinal products only if they are included in one of the following lists:

(a) the Union list of authorised food additives in Table 1, Part B, of Annex II to Regulation (EC) No 1333/2008, and those colours comply with the purity criteria and specifications laid down in Commission Regulation (EU) No 231/2012;

(b) the list of colours permitted for use in medicinal products other than those included in the Union list of authorised food additives established by the Commission pursuant to paragraph 3.

3. The Commission may establish a list of colours permitted for use in medicinal products other than those included in the Union list of authorised food additives.

The Commission shall, where applicable on the basis of an opinion of the Agency, adopt a decision as to whether the colour concerned is to be added to the list of colours referred to in the first subparagraph.

A colour may be added to the list of colours referred to in the first subparagraph only where the colour has been removed from the Union list of authorised food additives.

Where relevant, the list of colours referred to in the first subparagraph shall include purity criteria, specifications or restrictions applicable to the colours included in that list.

The list of colours referred to in the first subparagraph shall be established by way of implementing acts. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 217(2).

4. If a colour used in medicinal product is removed from the Union list of authorised food additives, on the basis of the scientific opinion of the EFSA, the Agency shall, on the request of the Commission or on its own initiative, without undue delay issue a scientific opinion on the use of the colour concerned in medicinal products, taking into account the opinion of the EFSA. The opinion of the Agency shall be adopted by the Committee for Medicinal Products for Human Use referred to in Article 155 of Regulation (EU) 2026/…[+] (the 'Committee for Medicinal Products for Human Use').

The Agency without undue delay shall send to the Commission its scientific opinion on the use of the colour concerned in medicinal products, together with a report on the assessment.

The Commission shall, on the basis of the Agency opinion, and without undue delay, decide whether the colour concerned can be used in medicinal products and, where applicable, include it in the list of colours referred to in paragraph 3, first subparagraph.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

5. If a colour has been removed from the Union list of authorised food additives for reasons that do not require an EFSA opinion, the Commission shall decide on the use of the colour concerned in medicinal products and, where applicable, include it in the list of colours referred to in paragraph 3, first subparagraph. The Commission may, in such cases, request an opinion from the Agency as regards the use of the colour in medicinal products.

6. A colour that has been removed from the Union list of authorised food additives can continue to be used as a colour in medicinal products until the Commission takes a decision on whether to include the colour in the list of colours permitted for use in medicinal products in accordance with paragraph 3.

7. Paragraphs 2 to 6 of this Article shall also apply to colours used in veterinary medicinal products as defined in Article 4, point (1), of Regulation (EU) 2019/6.

SECTION 5

ADAPTED DOSSIER REQUIREMENTS

Article 31

Adapted frameworks due to the characteristics inherent to or methods related to the medicinal product or to the category of medicinal products

1. Medicinal products or categories of medicinal products listed in Annex VII shall be subject to adapted scientific or technical requirements with regard to the authorisation, pharmacovigilance, control and use of those medicinal products or those categories of medicinal products ('adapted framework'). A medicinal product or category of medicinal products shall be listed in Annex VII where:

   (a) it is not possible to adequately assess or monitor the quality, safety and efficacy of the medicinal product or category of medicinal products by applying the requirements set out in this Directive, in Regulation (EC) No 1394/2007 or in Regulation (EU) 2026/…[+], due to scientific or technical characteristics inherent to the medicinal products or due to methods related to the medicinal product or category of medicinal products; and

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(b) the characteristics or methods related to the medicinal product or category of medicinal products contribute positively to the quality, safety and efficacy of the medicinal product or category of medicinal products as provided for in this Directive and in Regulation (EU) 2026/…[+] or make a major contribution to patient access to prevention, diagnosis, treatment or patient care.

2. The Commission is empowered to adopt delegated acts in accordance with Article 218, after having consulted the Agency and competent authorities of the Member States, to amend the list of medicinal products or categories of medicinal products in Annex VII in order to take account of scientific and technical progress.

3. The Commission is empowered to adopt delegated acts in accordance with Article 218, after having consulted the Agency and the competent authorities of the Member States, to supplement this Directive by laying down the adapted framework for medicinal products or categories of medicinal products listed in Annex VII as well as the technical documentation to be submitted by the marketing authorisation applicants for the medicinal product or category of medicinal products for which the adapted framework is laid down.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

The adapted framework may entail specific requirements and targeted technical adaptations to the requirements set out in this Directive and Regulation (EU) 2026/…[+] which are necessary for the purposes of assessing whether a marketing authorisation referred to in Article 6 of this Directive can be granted for a medicinal product or category of medicinal products listed in Annex VII and for their life-cycle management. The technical adaptations shall be proportionate to the risk and impact involved and shall be based on objective and scientific considerations. In particular, any technical adaptation shall ensure that the principles of quality, safety and efficacy set out in this Directive and in Regulation (EU) 2026/…[+] are respected. The adaptations shall be limited to the extent that such adaptations are strictly necessary and duly justified by the characteristics or methods related to the medicinal product or category of medicinal products. The Commission shall regularly review and evaluate the technical adaptations.

4. A marketing authorisation for a medicinal product subject to an adapted framework as referred to in paragraph 3 may be granted provided that the benefit-risk balance of the medicinal product is favourable.

5. Until the adoption of technical adaptations pursuant to paragraph 3 of this Article for a medicinal product or a category of medicinal products listed in Annex VII, an application for a marketing authorisation for the medicinal product may be submitted in accordance with Article 7(2).

6. When adopting delegated acts referred to in this Article, the Commission shall take into account any available information resulting from a regulatory sandbox established in accordance with Article 116 of Regulation (EU) 2026/…[+].

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

Chapter III
Procedures for national marketing authorisations

SECTION 1
GENERAL PROVISIONS

Article 32

Examination of marketing authorisation applications

1. In order to examine a marketing authorisation application submitted in accordance with Articles 7 and 10 to 15, the competent authority of the Member State:

   (a) shall verify that the particulars and documents submitted in support of the application comply with Articles 7 and 10 to 15 (‘validation of the application’), and examine whether the conditions for granting a marketing authorisation set out in Articles 46, 47 and 48 are complied with;

   (b) may submit the medicinal product, its starting materials or ingredients and, if need be, its intermediate products or other constituents, to testing by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose, in order to ensure that the control methods employed by the manufacturer of medicinal products and described in the particulars accompanying the marketing authorisation application in accordance with Annex I are satisfactory;

(c) may, where appropriate, require the marketing authorisation applicant to provide supplementary information in respect of the items listed in Articles 7 and 10 to 15;

(d) may consider and decide upon additional evidence that is available to the competent authority of that Member State, independently from the data submitted by the marketing authorisation applicant, inform the applicant of its decision and the grounds for that decision, and require the applicant to make changes to the summary of product characteristics;

(e) may, where appropriate, require the applicant to provide raw data concerning the pharmaceutical and non-clinical tests and the clinical studies referred to in Annex I.

2. Where, in the course of the validation of the application referred to in paragraph 1, point (a), the competent authority of the Member State considers that the marketing authorisation application is incomplete or contains deficiencies to the extent that it could prevent the evaluation of the application, it shall inform the applicant accordingly and shall set a time limit for submitting the missing particulars and documents.

If the marketing authorisation applicant fails to provide the missing particulars and documents within that time limit, the application shall be considered to have been withdrawn by the applicant.

3. Where the competent authority of the Member State avails itself of the option referred to in paragraph 1, point (c), the time limits laid down in Article 33 shall be suspended until such time as the supplementary information required has been provided or until the time granted to the applicant for giving explanations has expired.

4. Where, in the course of examining a marketing authorisation application, the competent authority of the Member State considers that the data submitted are not of sufficient quality or maturity for it to complete its examination of the application, the examination of the application can be terminated within 90 days of the date on which the competent authority of the Member State has verified that the particulars and documents submitted in support of the application comply with Article 7 and 10 to 15 (‘date of validation’).

Prior to terminating its examination of the marketing authorisation application, the competent authority of the Member State shall summarise the deficiencies in writing. On this basis, the competent authority of the Member State shall inform the marketing authorisation applicant accordingly and set a reasonable time limit to address the deficiencies. The examination of the marketing authorisation application shall be suspended until the marketing authorisation applicant addresses the deficiencies. If the marketing authorisation applicant fails to address those deficiencies within the time limit set by the competent authority of the Member State, the examination shall be terminated and the marketing authorisation application shall be considered to have been withdrawn by the marketing authorisation applicant.

5. When making public the information on the ERA and the antimicrobial stewardship plan referred to in Article 18, the competent authority of the Member State shall delete any information of a commercially confidential nature.

6. Where a potential serious risk to public health related to the reference medicinal product is examined under a specific procedure under this Directive or Regulation (EU) 2026/…[+], the Member States shall suspend the examination of any marketing authorisation application submitted under Articles 10 to 13 of this Directive that uses the same reference medicinal product until the end of the procedure related to the reference medicinal product.

7. Where the competent authorities of the Member States become aware that a marketing authorisation application is already being examined by a competent authority of another Member State for the same medicinal product, they shall refuse to validate the marketing authorisation application and shall advise the applicant to use the procedure referred to in Article 37 or 39.

8. Where the competent authorities of the Member States become aware that a Member State has already granted a marketing authorisation for the same medicinal product, they shall refuse to validate the marketing authorisation application unless it was submitted in accordance with the mutual recognition procedure as laid down in Article 39.

Article 33

Duration of examination of a marketing authorisation application

Member States shall take all appropriate measures to ensure that the procedure for granting a marketing authorisation for medicinal products is completed within 180 days of the date of validation of the marketing authorisation application.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

Article 34

Types of national marketing authorisation procedures

National marketing authorisations may be granted in accordance with the purely national procedure, as laid down in Article 35, the decentralised procedure, as laid down in Articles 36 and 37, or the mutual recognition procedure, as laid down in Articles 38 and 39.

SECTION 2

MARKETING AUTHORISATIONS VALID IN A SINGLE MEMBER STATE

Article 35

Purely national procedure

1. With a view to obtaining a national marketing authorisation for a medicinal product in one Member State, namely an authorisation under the purely national procedure, the marketing authorisation applicant shall submit an application to the competent authority of that Member State.

2. The competent authority of the Member State in which the marketing authorisation is applied for shall examine the marketing authorisation application in accordance with Articles 32 and 33, draw up an assessment report and adopt a decision to grant or refuse a marketing authorisation in accordance with Articles 46, 47 and 48 or Article 50, as applicable, and with applicable national provisions.

3. A marketing authorisation granted under the purely national procedure shall be valid only in the Member State of the competent authority that granted it.

SECTION 3

MARKETING AUTHORISATIONS VALID IN SEVERAL MEMBER STATES

Article 36

Scope of decentralised procedure

1. With a view to obtaining a national marketing authorisation for a medicinal product in several Member States in respect of the same medicinal product, the marketing authorisation applicant shall submit an application to the competent authorities of the Member States in which the applicant seeks to obtain a national marketing authorisation.

2. The competent authorities of the Member States concerned by the decentralised procedure shall examine the marketing authorisation application in accordance with Articles 32, 33 and 37, and adopt a decision to grant or refuse a marketing authorisation in accordance with Articles 46, 47 and 48 or Article 50, as applicable.

3. Marketing authorisations granted under the decentralised procedure shall be valid only in those Member States whose competent authorities granted the marketing authorisations.

Article 37

Decentralised procedure

1. The marketing authorisation applicant under the decentralised procedure shall submit a marketing authorisation application based on an identical dossier:

   (a) to the competent authority of the Member State chosen by the applicant to draw up the assessment report on the medicinal product in accordance with Article 46(3) and to act in accordance with this Section (‘reference Member State for the decentralised procedure’), and

   (b) to the competent authorities of the other Member States concerned by the decentralised procedure.

2. The marketing authorisation application shall contain:

   (a) the particulars and documents referred to in Articles 7, 10 to 15 and 65;

   (b) a list of the Member States concerned by the decentralised procedure.

3. The marketing authorisation applicant shall inform all the competent authorities of all Member States when submitting an application pursuant to paragraph 1.

If necessary to meet the needs of patients in a Member State, the competent authority of that Member State may request that its Member State become a Member State concerned by the decentralised procedure and shall, within 30 days of the date of submission of the marketing authorisation application, inform the marketing authorisation applicant and the competent authority of the reference Member State for the decentralised procedure of that request. The marketing authorisation applicant shall provide the competent authority of that Member State with the marketing authorisation application without undue delay, on receipt of which that Member State shall be considered as a Member State concerned by the decentralised procedure.

4. Where, in the course of the validation of the application, the competent authority of the reference Member State for the decentralised procedure considers that the marketing authorisation application is incomplete or contains deficiencies to the extent that it could prevent the evaluation of the application, it shall inform the applicant accordingly and shall set a reasonable time limit for submitting the missing particulars and documents.

If the marketing authorisation applicant fails to provide the missing particulars and documents within that time limit, the application shall be considered to have been withdrawn by the applicant in the reference Member State for the decentralised procedure and in the other Member States concerned by the decentralised procedure.

5. Where, in the course of examining a marketing authorisation application, the competent authority of the reference Member State for the decentralised procedure considers that the data submitted are not of sufficient quality or maturity for it to complete its examination of the application, the examination of the application can be terminated within 90 days of the date of validation of the application.

Prior to terminating its examination of the marketing authorisation application, the competent authority of the reference Member State for the decentralised procedure shall summarise the deficiencies in writing. On this basis, the competent authority of the reference Member State for the decentralised procedure shall inform the marketing authorisation applicant and the competent authorities of the Member States concerned by the decentralised procedure accordingly and set a time limit to address the deficiencies. The examination of the marketing authorisation application shall be suspended until the marketing authorisation applicant addresses those deficiencies. If the marketing authorisation applicant fails to address those deficiencies within that time limit set by the competent authority of the reference Member State for the decentralised procedure, the examination of the application shall be terminated and the marketing authorisation application shall be considered to have been withdrawn by the applicant in the reference Member State for the decentralised procedure and in the other Member States concerned by the decentralised procedure.

The competent authority of the reference Member State for the decentralised procedure shall inform the competent authorities of the other Member States concerned by the decentralised procedure and the marketing authorisation applicant accordingly.

6. Within 105 days of the date of validation of the application, the competent authority of the reference Member State for the decentralised procedure shall draw up an assessment report, the summary of product characteristics, the labelling and the package leaflet and shall send them to the other Member States concerned by the decentralised procedure and to the marketing authorisation applicant.

7. Within 75 days of receipt of the assessment report, the summary of product characteristics, the labelling and the package leaflet, and unless Article 41 applies, the competent authorities of the Member States concerned by the decentralised procedure shall approve the assessment report, the summary of product characteristics, the labelling and the package leaflet and shall inform the competent authority of the reference Member State for the decentralised procedure accordingly. The competent authority of the reference Member State for the decentralised procedure shall acknowledge the agreement of all Member States concerned, close the procedure and inform the marketing authorisation applicant accordingly.

8. Within seven days of receipt of the information under paragraph 7, the marketing authorisation applicant shall submit high quality translations of the summary of product characteristics, the labelling and the package leaflet to the competent authority of the reference Member State for the decentralised procedure and each of the competent authorities of the other Member States concerned by the decentralised procedure.

9. Within 30 days of acknowledgement of the agreement referred to in paragraph 7 of this Article, the competent authorities of the reference Member States for the decentralised procedure and the other Member States concerned by the decentralised procedure shall adopt a decision in accordance with Articles 46, 47 and 48 and in conformity with the approved assessment report, summary of product characteristics, labelling and package leaflet.

SECTION 4

MUTUAL RECOGNITION OF NATIONAL MARKETING AUTHORISATIONS

Article 38

Scope of mutual recognition procedure

1. Where, at the time an application for a national marketing authorisation is submitted in a given Member State, a national marketing authorisation has already been granted for the same medicinal product in one or more other Member States in accordance with Articles 46, 47 and 48, the national marketing authorisation that has already been granted shall be recognised in accordance with Article 39 in the Member State where the application for a national marketing authorisation is submitted.

2. An application for mutual recognition of a national marketing authorisation that has been granted in a Member State in accordance with Articles 46, 47 and 48 shall be submitted in accordance with Article 39.

Article 39

Mutual recognition procedure

1. An application for mutual recognition of a national marketing authorisation shall be submitted to:

   (a) the competent authority of one of the Member States that granted the national marketing authorisation (‘reference Member State for the mutual recognition procedure’), and

   (b) the competent authorities of the Member States concerned by the mutual recognition procedure, namely those in which the applicant seeks to obtain a national marketing authorisation under the mutual recognition procedure.

2. The application shall include a list of the Member States concerned by the mutual recognition procedure.

3. For a period of one year from the granting of a national marketing authorisation, the competent authority of the reference Member State for the mutual recognition procedure shall refuse applications for mutual recognition of that national marketing authorisation.

   However, where the competent authority of the reference Member State for the mutual recognition procedure is informed by the competent authority of another Member State that that Member State has an interest in that medicinal product, the first subparagraph shall not apply.

4. The marketing authorisation applicant shall inform all the competent authorities of all Member States when submitting an application pursuant to paragraph 1.

If necessary to meet the needs of patients in a Member State, the competent authority of that Member State may request that its Member State become a Member State concerned by the mutual recognition procedure and shall, within 30 days of the date of submission of the marketing authorisation application, inform the marketing authorisation applicant and the competent authority of the reference Member State for the mutual recognition procedure of that request. The applicant shall provide the competent authority of that Member State with the application for mutual recognition without undue delay, on receipt of which that Member State shall be considered as a Member State concerned by the mutual recognition procedure.

5. The competent authority of the reference Member State for the mutual recognition procedure shall send the assessment report together with the approved summary of product characteristics, labelling and package leaflet to the Member States concerned by the mutual recognition procedure and to the applicant within 30 days of the date of validation of the application for mutual recognition. Where a Member State concerned by the mutual recognition procedure requests that the assessment report be updated, the procedure may be extended to 90 days.

6. Within 60 days of receipt of the assessment report, the summary of product characteristics, the labelling and the package leaflet, and unless Article 41 applies, the competent authorities of the Member States concerned by the mutual recognition procedure shall approve the assessment report, the summary of product characteristics, the labelling and the package leaflet and shall inform the competent authority of the reference Member State for the mutual recognition procedure accordingly.

7. The competent authority of the reference Member State for the mutual recognition procedure shall acknowledge the agreement between the reference Member State for the mutual recognition procedure and the Member States concerned by the mutual recognition procedure, close the procedure and inform the applicant accordingly.

8. Within seven days of receipt of the information under paragraph 7, the applicant shall provide high quality translations of the summary of product characteristics, the labelling and the package leaflet to each of the competent authorities of the Member States concerned by the mutual recognition procedure.

9. Within 30 days of acknowledgement of the agreement referred to in paragraph 7 of this Article, the competent authorities of the Member States concerned by the mutual recognition procedure shall adopt a decision in accordance with Articles 46, 47 and 48 and in conformity with the approved assessment report, summary of product characteristics, labelling and package leaflet.

SECTION 5

COORDINATION OF NATIONAL MARKETING AUTHORISATIONS

Article 40

Coordination group for decentralised and mutual recognition procedures

1. A coordination group for decentralised and mutual recognition procedures (the 'coordination group') shall be set up for the following purposes:

   (a) to examine any question relating to a national marketing authorisation for a medicinal product in two or more Member States in accordance with the procedures laid down in Sections 3 and 4 and in this Section of this Chapter, and in Article 98;

   (b) to examine questions related to the pharmacovigilance of medicinal products covered by national marketing authorisations, in accordance with Articles 112, 114, 116, 120 and 125;

   (c) to examine questions relating to variations of national marketing authorisations, in accordance with Article 95(1).

   (d) to establish and publish a list of medicinal products for which a harmonised summary of product characteristics is to be drawn up, in accordance with Article 43;

   (e) to harmonise the summary of product characteristics, in accordance with Article 43.

For the purpose of carrying out its pharmacovigilance tasks referred to in the first subparagraph, point (b), such as approving risk management systems and monitoring their effectiveness, the coordination group shall rely on the scientific assessment and recommendations of the Pharmacovigilance Risk Assessment Committee referred to in Article 156 of Regulation (EU) 2026/…[+] (the 'Pharmacovigilance Risk Assessment Committee').

2. The coordination group shall be composed of one representative per Member State, appointed for a renewable period of three years. Member States may appoint an alternate for a renewable period of three years. Members of the coordination group may arrange to be accompanied by experts.

For the purpose of carrying out their tasks, members of the coordination group and experts shall rely on the scientific and regulatory resources available to competent authorities of the Member States. Each competent authority of the Member State shall monitor the level of expertise of the evaluations carried out and facilitate the activities of appointed coordination group members and experts.

Article 154 of Regulation (EU) 2026/…[+] shall apply to the coordination group as regards transparency and the independence of its members.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

3. The Agency shall provide the secretariat of the coordination group. The coordination group shall draw up its own rules of procedure, which shall enter into force after a favourable opinion has been given by the Commission. Those rules of procedure shall be made publicly available.

4. The Executive Director of the Agency or the representative of the Executive Director and representatives of the Commission shall be entitled to attend all meetings of the coordination group.

5. The members of the coordination group shall ensure that there is appropriate coordination between the tasks of that group and the work of competent authorities of the Member States, including the consultative bodies concerned with national marketing authorisations.

6. Unless otherwise provided for in this Directive, within the coordination group, all Member States representatives shall use their best endeavours to reach a position by consensus on the action to be taken. If such a consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall prevail.

7. Members of the coordination group shall be required, even after their duties have ceased, not to disclose information of the kind covered by the obligation of professional secrecy.

Article 41

Divergent positions of Member States in a decentralised or mutual recognition procedure

1. If, at the end of the period laid down in Article 37(7) or in Article 39(6), there is disagreement between Member States on whether the national marketing authorisation can be granted, on the grounds of potential serious risk to public health, the Member State concerned shall provide a detailed explanation of the points of disagreement and the reasons for its position to the reference Member State for the decentralised procedure or for the mutual recognition procedure (the 'reference Member State'), to the Member States concerned by the decentralised procedure or by the mutual recognition procedure (the 'Member States concerned') and to the applicant. The points of disagreement shall be referred to the coordination group without undue delay.

2. Guidelines to be adopted by the Commission shall define a potential serious risk to public health.

3. Within the coordination group, Member States shall use their best endeavours to reach an agreement on the action to be taken. They shall provide the marketing authorisation applicant with an opportunity to make its point of view known orally or in writing. If, within 60 days of the communication of the points of disagreement, the Member States reach an agreement by consensus, the reference Member State shall acknowledge the agreement, close the procedure and inform the marketing authorisation applicant accordingly. The procedure laid down in Article 37(9) or in Article 39(9) shall apply.

4. If within the 60-day period laid down in paragraph 3 of this Article, an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group, with a detailed description of the matters on which the other Member States have been unable to reach an agreement and of all the divergent positions of Member States presented, shall be forwarded to the Commission. The coordination group may recommend that the Commission refers the matter to the Committee for Medicinal Products for Human Use. The Commission shall apply the procedure laid down in Article 45. Where the Commission, on its own initiative or based on the recommendation of the coordination group, considers that the matter is to be referred to the Committee for Medicinal Products for Human Use, Article 44 shall also apply.

5. In the circumstances referred to in paragraph 4 of this Article, Member States that have approved the assessment report, the summary of product characteristics, the labelling and the package leaflet of the reference Member State may, at the request of the applicant, authorise the medicinal product without waiting for the outcome of the procedure laid down in Article 45. In that event, the national marketing authorisation shall be granted without prejudice to the outcome of that procedure.

Article 42

Referral procedure for divergent decisions by Member States

Where applications for a national marketing authorisation have been submitted in accordance with Articles 7 and 10 to 15 for a particular medicinal product and Member States have adopted divergent decisions concerning the national marketing authorisation, its variation, suspension or revocation or the summary of product characteristics, the competent authority of the Member State or the Commission may refer the matter to the Committee for Medicinal Products for Human Use for the application of the procedure laid down in Articles 44 and 45.

Article 43

Harmonisation of summary of product characteristics

1. In order to promote the harmonisation of national marketing authorisations for medicinal products throughout the Union, the competent authorities of the Member States may, each year, propose to the coordination group a list of medicinal products for which a harmonised summary of product characteristics is to be drawn up.

2. The coordination group may establish a list of medicinal products for which a harmonised summary of product characteristics is to be drawn up, taking into account the proposals from the competent authorities of all Member States, and shall decide on the harmonisation of summary of product characteristics for those medicinal products and shall inform the Commission.

3. If, within the coordination group, the Member States represented reach an agreement by consensus on the action to be taken, the chairman shall acknowledge the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to vary the marketing authorisations concerned in accordance with the timetable for implementation determined in the agreement. The marketing authorisation holder shall submit to the competent authorities of the Member States an appropriate application for a variation of the marketing authorisation, including an updated summary of product characteristics and an updated package leaflet within the determined timetable for implementation.

4. If, within the coordination group, the Member States represented cannot reach an agreement by consensus, the position of the majority of the Member States represented together with a detailed description of the matters on which the other Member States have been unable to reach agreement and of all the divergent positions of Member States presented, shall be forwarded to the Commission. The Commission shall apply the procedure laid down in Article 45. Where the Commission, on its own initiative or based on the recommendation of the coordination group, considers that the matter is to be referred to the Committee for Medicinal Products for Human Use, Article 44 shall also apply.

Article 44

Referral to the Committee for Medicinal Products for Human Use

1. Where a matter is referred to the Committee for Medicinal Products for Human Use, the Committee for Medicinal Products for Human Use shall consider the matter and shall issue a reasoned opinion within 60 days of the date when the matter was referred to it.

   However, as regards matters referred to the Committee for Medicinal Products for Human Use in accordance with Article 42, Article 43(4) or Article 98, the period referred to in the first subparagraph of this paragraph may be extended by the Committee for Medicinal Products for Human Use for a further period of up to 90 days.

   On a proposal from its chairperson, the Committee for Medicinal Products for Human Use may agree to a shorter deadline than that provided for in the first subparagraph of this paragraph.

2. In order to consider the matter, the Committee for Medicinal Products for Human Use shall appoint one of its members to act as rapporteur. The Committee for Medicinal Products for Human Use may also appoint individual experts to advise it on specific questions. When appointing experts, the Committee for Medicinal Products for Human Use shall define their tasks and specify the time limit for the completion of those tasks.

3. Before issuing its opinion, the Committee for Medicinal Products for Human Use shall provide the marketing authorisation applicant or the marketing authorisation holder with an opportunity to present written or oral explanations within a time limit which it shall specify.

The opinion of the Committee for Medicinal Products for Human Use shall be accompanied by a summary of product characteristics, the labelling and the package leaflet.

If necessary, the Committee for Medicinal Products for Human Use may call upon any other person to provide information relating to the matter and may convene a public hearing in accordance with Article 153(1) of Regulation (EU) 2026/…[+].

The Agency shall, in consultation with the parties concerned, draw up rules of procedure on the organisation and conduct of public hearings, in accordance with Article 153(1) of Regulation (EU) 2026/…[+].

The Committee for Medicinal Products for Human Use may suspend the time limits referred to in paragraph 1 of this Article in order to allow the marketing authorisation applicant or the marketing authorisation holder to prepare explanations.

4. The Agency shall without undue delay inform the marketing authorisation applicant or the marketing authorisation holder where the opinion of the Committee for Medicinal Products for Human Use concludes that:

(a) the marketing authorisation application does not satisfy the criteria for a national marketing authorisation;

(b) the summary of product characteristics proposed by the marketing authorisation applicant or the marketing authorisation holder in accordance with Article 65 is to be amended;

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(c) the national marketing authorisation is to be granted subject to certain conditions, that are considered essential for the safe and effective use of the medicinal product, including pharmacovigilance;

(d) a national marketing authorisation is to be suspended, varied or revoked;

(e) the medicinal product satisfies the conditions set out in Article 85 regarding medicinal products addressing an unmet medical need.

Where the marketing authorisation applicant or the marketing authorisation holder intends to request a re-examination of the opinion of the Committee for Medicinal Products for Human Use, the marketing authorisation applicant or the marketing authorisation holder shall notify the Agency in writing of its intention within 12 days of receipt of the opinion of the Committee for Medicinal Products for Human Use and shall forward the detailed grounds for the request to the Agency within 60 days of receipt of the opinion.

Within 60 days of receipt of the grounds for the request, the Committee for Medicinal Products for Human Use shall re-examine its opinion in accordance with Article 13(2), third subparagraph, of Regulation (EU) 2026/…[+]. The reasons for the conclusion reached in its final opinion following that re-examination shall be annexed to the assessment report referred to in Article 13(3) of Regulation (EU) 2026/…[+].

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

5. Within 12 days of the issuance by the Committee for Medicinal Products for Human Use of its final opinion, the Agency shall forward it to the competent authorities of the Member States, to the Commission and to the marketing authorisation applicant or the marketing authorisation holder, together with a report describing the assessment of the medicinal product and stating the reasons for its conclusions.

In the event of an opinion in favour of granting or maintaining a marketing authorisation to place the medicinal product concerned on the market, the following documents shall be annexed to the final opinion:

(a) a summary of product characteristics, as referred to in Article 65;

(b) the details of any conditions affecting the marketing authorisation within the meaning of paragraph 4, first subparagraph, point (c);

(c) the details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product;

(d) the labelling and the package leaflet.

Article 45

Commission decision

1. Within 12 days of receipt of the opinion of the Committee for Medicinal Products for Human Use or the position of the majority of the Member States represented within the coordination group, as set out in Article 41(4), the Commission shall submit to the Standing Committee on Medicinal Products for Human Use referred to in Article 217(1) a draft of the decision on the application concerned ('draft decision'), on the basis of the requirements set out in this Directive.

   In duly justified cases, the Commission may refer the opinion of the Committee for Medicinal Products for Human Use or the position of the majority of the Member States represented within the coordination group, back to the Agency or to the coordination group, as applicable, for further consideration.

   Where a draft decision envisages the granting of a marketing authorisation, it shall include or make reference to the documents referred to in Article 41(5) or 44(5), second subparagraph.

   Where a draft decision diverges from the opinion of the Committee for Medicinal Products for Human Use or from the position of the majority of the Member States represented within the coordination group, the Commission shall provide a detailed explanation of the reasons for that divergence.

   The Commission shall send the draft decision to the competent authorities of the Member States and to the marketing authorisation applicant or the marketing authorisation holder.

2. The Commission shall, by means of implementing acts, adopt a final decision within 12 days after obtaining the opinion of the Standing Committee on Medicinal Products for Human Use.

Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 217(2) and (3).

3. Where a Member State raises important new questions of a scientific or technical nature that have not been addressed in the opinion issued by the Committee for Medicinal Products for Human Use or in the position of the majority of the Member States represented within the coordination group, the Commission may refer the marketing authorisation application back to the Agency or to the coordination group, as applicable, for further consideration. In that case, the procedures set out in paragraphs 1 and 2 shall start again upon reception of the reply of the Agency or of the coordination group.

4. The decision referred to in paragraph 2 shall be addressed to all Member States and forwarded for information to the marketing authorisation applicant or to the marketing authorisation holder. The Member States concerned and the reference Member State shall adopt a decision to either grant, suspend, refuse or revoke the marketing authorisation, or vary its terms as necessary to comply with the decision referred to in paragraph 2 within 30 days of its notification. In the decision to grant, suspend, refuse, revoke or vary the marketing authorisation, the Member States shall refer to the decision adopted pursuant to paragraph 2. They shall inform the Agency or the coordination group accordingly, as applicable.

5. Where the procedure laid down in Article 44 and in this Article is initiated pursuant to Article 98 and the scope thereof includes medicinal products covered by a centralised marketing authorisation pursuant to Article 98(2), second subparagraph, the Commission shall, where necessary, adopt decisions to vary, suspend or revoke the marketing authorisations or to refuse the renewal of the marketing authorisations concerned in accordance with this Article.

SECTION 6

RESULTS OF EXAMINATION OF A NATIONAL MARKETING AUTHORISATION APPLICATION

Article 46

Granting of a national marketing authorisation

1. When the competent authority of a Member State grants a national marketing authorisation, it shall inform the marketing authorisation applicant of the summary of product characteristics, the package leaflet, the labelling as well as any conditions established in accordance with Articles 47 and 48 together with any deadlines for the fulfilment of those conditions.

2. The competent authorities of the Member States shall take all necessary measures to ensure that the information given in the summary of product characteristics complies with that accepted when the national marketing authorisation is granted or subsequently.

3. The competent authorities of the Member States shall draw up an assessment report and make comments on the file as regards the results of the pharmaceutical and non-clinical tests, the clinical studies, the risk management system, the ERA and the pharmacovigilance system of the medicinal product concerned.

4. The competent authorities of the Member States shall make the assessment report publicly available without undue delay, together with the reasons for their opinion, after deletion of any information of a commercially confidential nature. Reasons shall be provided separately for each therapeutic indication applied for.

5. The public assessment report referred to in paragraphs 3 and 4 shall include a summary written in a manner that is understandable to the public. The summary shall contain, in particular, a section relating to the conditions of use of the medicinal product.

6. The competent authorities of the Member States shall, without undue delay, make publicly available the national marketing authorisation together with the summary of product characteristics, the package leaflet, the antimicrobial stewardship plan and special information requirements referred to in Article 18(1), points (a) and (b), as well as any conditions established in accordance with Articles 47 and 48 and any obligations imposed subsequently in accordance with Article 89, together with any deadlines for the fulfilment of those conditions and obligations for each medicinal product that they have authorised.

Article 47

National marketing authorisation subject to conditions

1. A national marketing authorisation for a medicinal product may be granted subject to one or more of the following conditions:

   (a) to take certain measures to ensure the safe use of the medicinal product to be included in the risk management system;

   (b) to conduct post-authorisation safety studies;

   (c) to comply with obligations regarding the recording or reporting of suspected adverse reactions that are stricter than those referred to in Chapter IX;

   (d) to comply with any other conditions or restrictions with regard to the safe and effective use of the medicinal product;

   (e) to have an adequate pharmacovigilance system in place;

   (f) to conduct post-authorisation efficacy studies where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed;

   (g) in the case of medicinal products for which there is substantial uncertainty as to the surrogate endpoint in relation to the expected health outcome, to impose, where appropriate and relevant for the benefit-risk balance, a post-authorisation obligation to substantiate the clinical benefit;

(h) to conduct post-authorisation ERA studies, to collect monitoring data or information on use, or to implement appropriate risk mitigation measures, where identified or potential concerns about risks to the environment or public health, including antimicrobial resistance, need to be further investigated or mitigated after the medicinal product has been marketed;

(i) to conduct post-authorisation studies in order to improve the safe and effective use of the medicinal product;

(j) where appropriate, to carry out medicinal product-specific validation studies to replace animal-based control methods with non-animal-based control methods.

An obligation to conduct post-authorisation efficacy studies referred to in the first subparagraph, point (f), shall be based on the delegated acts adopted pursuant to Article 90.

2. The national marketing authorisation shall lay down deadlines for the fulfilment of the conditions referred to in paragraph 1, first subparagraph, where necessary.

Article 48

National marketing authorisation under exceptional circumstances

1. In exceptional circumstances where, with regard to a marketing authorisation application under Article 7 for a medicinal product or an application for a variation of an existing marketing authorisation under Article 94 for a new therapeutic indication, an applicant is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, the competent authority of the Member State may, by way of derogation from Article 7, grant a national marketing authorisation under Article 46, subject to specific conditions, where the following requirements are met:

   (a) the applicant has demonstrated, in accordance with Annex II, that there are objective and verifiable reasons why it is unable to submit comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use;

   (b) except for the data referred to in point (a), the application is complete and satisfies all the requirements of this Directive;

   (c) specific conditions are included in the decision of the competent authorities of the Member States, in particular to ensure the safety of the medicinal product as well to ensure that the marketing authorisation holder notifies to the competent authorities of the Member States any incident relating to its use and takes appropriate action where necessary.

2. The maintenance of the authorised new therapeutic indication and of the validity of the national marketing authorisation under exceptional circumstances shall be subject to a reassessment of the conditions set out in paragraph 1, carried out in accordance with paragraph 3.

3. The competent authorities of the Member States shall reassess the conditions set out in paragraph 1 two years after the date when the new therapeutic indication was authorised or the national marketing authorisation was granted, or within a shorter deadline specified by the competent authorities of the Member States, and thereafter at a risk-based frequency to be determined by the competent authorities of the Member States and specified in the national marketing authorisation.

The reassessment of the conditions shall be conducted on the basis of an application by the marketing authorisation holder to maintain the authorised new therapeutic indication or to maintain the validity of the national marketing authorisation under exceptional circumstances.

Article 49

Validity and renewal of national marketing authorisations

1. Without prejudice to paragraph 4, the national marketing authorisation for a medicinal product shall be valid for an unlimited period.

By way of derogation from the first subparagraph, a national marketing authorisation granted in accordance with Article 48(1) shall be valid for five years.

By way of derogation from the first subparagraph, the competent authority of the Member State may decide at the time of granting the national marketing authorisation, on objectively and duly justified grounds relating to safety of the medicinal product, to limit the validity of the national marketing authorisation to five years.

2. The marketing authorisation holder may submit an application for a renewal of a national marketing authorisation as referred to in paragraph 1, second or third subparagraph. Such application shall be submitted at least nine months before the validity of the national marketing authorisation expires.

3. Once the application for a renewal has been submitted within the time limit provided for in paragraph 2, the national marketing authorisation shall remain valid until the competent authority of the Member State adopts a decision on the renewal.

4. The competent authority of the Member State may renew the national marketing authorisation on the basis of a re-evaluation of the benefit-risk balance. Once renewed, the national marketing authorisation shall be valid for an unlimited period.

Article 50

Refusal of a national marketing authorisation

1. The competent authority of the Member State shall refuse to grant a national marketing authorisation where, after verification of the particulars and documents referred to in Article 7 and subject to the specific requirements laid down in Articles 10 to 15, it considers that:

   (a) any of the particulars or documents submitted in support of the application does not comply with Article 7, paragraphs 1 to 6, or Articles 10 to 15;

   (b) the benefit-risk balance is not favourable;

   (c) the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product;

   (d) the qualitative and quantitative composition of the medicinal product is not as declared;

   (e) the ERA is incomplete or insufficiently substantiated or the risks identified in the ERA have not been sufficiently addressed by the applicant, including through risk mitigation measures, unless the applicant has duly justified and substantiated the reasons for the incomplete or insufficiently substantiated ERA, and the competent authority of the Member State considers that the marketing authorisation can be granted subject to the condition that post-authorisation ERA studies be conducted or risk mitigation measures be implemented, as referred to in Article 47(1), point (h).

(f) the labelling and the package leaflet proposed by the applicant do not comply with Chapter VI or they are not in accordance with the particulars listed in the summary of product characteristics.

2. The marketing authorisation applicant or the marketing authorisation holder shall be responsible for the accuracy of the particulars and documents submitted.

SECTION 7

SPECIFIC REQUIREMENTS FOR PAEDIATRIC MEDICINAL PRODUCTS

Article 51

Compliance with the agreed paediatric investigation plan

1. The competent authority of the Member State in which a marketing authorisation application or an application for a variation of a marketing authorisation is submitted under this Chapter or Chapter VIII, shall verify whether it complies with the requirements laid down in Article 7(5).

2. Where a marketing authorisation application or an application for a variation of a marketing authorisation is submitted in accordance with the procedure set out in this Chapter, Section 3 or 4, the verification of compliance, including, as appropriate, requesting an opinion of the Agency in accordance with paragraph 3, point (b), shall be conducted by the reference Member State.

3. The Committee for Medicinal Products for Human Use may, in the following cases, be requested to provide its opinion as to whether studies conducted by the applicant are in compliance with the paediatric investigation plan agreed in accordance with Article 79 of Regulation (EU) 2026/…[+]:

(a) by the applicant, prior to submitting a marketing authorisation application or an application for a variation of a marketing authorisation;

(b) by the competent authority of the Member State, when validating a marketing authorisation application or an application for a variation of a marketing authorisation that does not already include such an opinion.

4. In the case of a request in accordance with paragraph 3, point (a), the applicant shall not submit its application until the Committee for Medicinal Products for Human Use has provided its opinion, and a copy thereof shall be annexed to the application.

5. Member States shall take due account of any opinion provided in accordance with paragraph 3.

6. When the competent authority of the Member State, during the scientific assessment of a valid application for a marketing authorisation or for a variation of a marketing authorisation, concludes that the studies are not in conformity with the agreed paediatric investigation plan, the medicinal product shall not be eligible for the rewards and incentives provided for in Article 88.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

Article 52

Data deriving from a paediatric investigation plan

1. Where a marketing authorisation or a variation of a marketing authorisation is granted in accordance with this Chapter or Chapter VIII:

   (a) the results of all studies conducted in compliance with an agreed paediatric investigation plan as referred to in Article 7(5), point (a), shall be included in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned; or

   (b) any waiver as referred to in Article 7(5), point (b), shall be recorded in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.

2. If the application complies with all the measures contained in the agreed completed paediatric investigation plan and if the summary of product characteristics reflects the results of studies conducted in compliance with that agreed paediatric investigation plan, the competent authority of the Member State shall include within the marketing authorisation a statement indicating compliance of the application with the agreed completed paediatric investigation plan. The competent authority of the Member State shall make the conclusions of the assessment regarding compliance with the agreed completed paediatric investigation plan publicly available.

3. An application for new therapeutic indications, including paediatric indications, new pharmaceutical forms, new strengths and new routes of administration of medicinal products authorised in accordance with this Chapter or Chapter VIII and which are protected either by a supplementary protection certificate under Regulation (EC) No 469/2009, or by a patent which qualifies for the granting of a supplementary protection certificate, may be referred to the Committee for Medicinal Products for Human Use under the procedure laid down in Articles 44 and 45.

4. The procedure referred to in paragraph 3 shall be limited to the assessment of the specific section of the summary of product characteristics to be varied.

Chapter IV
Prescription status

Article 53

Prescription status of medicinal products

1. When a marketing authorisation is granted, the competent authorities shall, by applying the criteria laid down in Article 54, specify the prescription status of the medicinal product as:

   (a) a medicinal product subject to medical prescription; or

   (b) a medicinal product not subject to medical prescription.

2. The competent authorities of the Member States may provide for sub-categories of medicinal products that are subject to the following prescription status:

(a) medicinal products subject to medical prescription for renewable or non-renewable delivery;

(b) medicinal products subject to special medical prescription;

(c) medicinal products subject to restricted medical prescription, reserved for use in specific specialised areas.

Article 54

Medicinal products subject to medical prescription

1. A medicinal product shall be subject to medical prescription pursuant to Article 53(1), point (a), where it:

(a) is likely to present a danger either directly or indirectly, even when used correctly, if used without medical supervision;

(b) is frequently and to a very wide extent used incorrectly, and as a result is likely to present a direct or indirect danger to human health;

(c) contains substances or preparations thereof, the activity or adverse reactions of which require further investigation;

(d) is normally prescribed by a doctor to be administered parenterally;

(e) is an antimicrobial; or

(f) contains an active substance which is persistent, bioaccumulative and toxic; very persistent and very bioaccumulative; persistent, mobile and toxic; or very persistent and very mobile, and for which medical prescription is required as a risk minimisation measure with regard to the environment, unless other circumstances of use justify otherwise.

2. Member States may set one or more of the following conditions to the prescription of medicinal products referred to in paragraph 1, point (e), or to the prescription of medicinal products containing active substances referred to in paragraph 1, point (f):

(a) limiting the quantities prescribed to the amount required for the treatment or therapy concerned;

(b) restricting the validity of the medical prescription; or

(c) subjecting certain antimicrobials to special medical prescription or restricted medical prescription.

3. Where the Member State provides for a sub-category of medicinal products to be subject to special medical prescription, it shall take account of whether:

(a) the medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of international conventions;

(b) the medicinal product is likely, if incorrectly used, to present a substantial risk of abuse of medicinal products, to lead to addiction or be misused for illegal purposes; or

(c) the medicinal product contains a substance that, by reason of its novelty or properties, could, as a precautionary measure, be considered as belonging to the group set out in point (b).

4. Where the Member State provides for a sub-category of medicinal products to be subject to restricted medical prescription, it shall take account of whether:

(a) the medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments that can only be followed in a hospital environment;

(b) the medicinal product is used in the treatment of conditions that can only be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, irrespective of where the medicinal product is administered and of where follow-up takes place;

(c) the medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring a medical prescription drawn up as required by a specialist and special supervision throughout the treatment.

5. The competent authority of a Member State may waive application of paragraphs 1, 3 and 4, taking into account:

(a) the maximum single dose, the maximum daily dose, the strength, the pharmaceutical form, certain types of packaging; or

(b) except for medicinal products referred to in paragraph 1, point (e), other circumstances of use that it has specified.

6. The competent authority of a Member State may waive application of paragraphs 1, 3 and 4 for medicinal products referred to in paragraph 1, point (e), for topical use.

7. If a Member State does not provide for sub-categories of medicinal products, the competent authority of that Member State shall nevertheless take into account the criteria laid down in paragraphs 3 and 4 of this Article in determining whether a given medicinal product is a medicinal product subject to medical prescription.

Article 55

Medicinal products not subject to medical prescription

A medicinal product shall not be subject to medical prescription if the medicinal product does not meet the criteria in Article 54(1), (3) and (4) or if Article 54(5) or (6) is applicable.

Article 56

Amendment of prescription status

When new facts are brought to their attention, the competent authorities shall examine and, as appropriate, amend the prescription status of a medicinal product by applying the criteria listed in Article 54.

In the case of a potential, expected or actual shortage of a medicinal product that puts patients' needs or public health at risk, the competent authorities of the Member States may temporarily amend the prescription status of a medicinal product from 'not subject to medical prescription' to 'subject to medical prescription' or from 'subject to medical prescription' to 'subject to restricted medical prescription'. The amendment shall be withdrawn as soon as the shortage or risk of shortage ceases.

Article 57

Data protection of evidence for the change of prescription status

Where a change of prescription status of a medicinal product has been authorised on the basis of significant non-clinical tests or clinical studies, the competent authority of the Member State, or the Agency, as applicable, shall not refer to the results of those tests or studies when examining an application by another marketing authorisation applicant for or marketing authorisation holder for a change of prescription status of the same substance for one year after the initial change was authorised.

Chapter V

Obligations and liability of the marketing authorisation holder

Article 58

General obligations

1. Where a marketing authorisation has been granted, the marketing authorisation holder shall be responsible for making the medicinal product that is covered by the marketing authorisation available on the market. The designation of a marketing authorisation holder representative shall not relieve the marketing authorisation holder of its legal responsibility.

2. The holder of a marketing authorisation for a medicinal product placed on the market in a Member State shall notify the competent authority of that Member State of the date of placing on the market in that Member State, taking into account the various presentations authorised.

3. Where a marketing authorisation is withdrawn, all relevant provisions of this Directive and of Regulation (EU) 2026/…[+] shall continue to apply to the medicinal product that was placed on the market under that marketing authorisation before the date of the withdrawal for an appropriate period. That period shall be approved by the competent authority prior to the withdrawal of the marketing authorisation.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

4. The holder of a marketing authorisation for a medicinal product placed on the market in a Member State shall, within the limits of its responsibility, ensure appropriate and continued supplies of that medicinal product to wholesale distributors, pharmacies or other persons authorised to supply medicinal products so that the needs of patients in that Member State are met.

The arrangements for implementing the first subparagraph shall be justified on grounds of public health protection and be proportionate in relation to the objective of such protection, in accordance with the TFEU, particularly as regards the free movement of goods and competition.

5. The marketing authorisation holder shall, at all stages of manufacturing and distribution, ensure and verify that the starting materials, the ingredients of the medicinal products and the medicinal products themselves are in compliance with the requirements of this Directive and, where relevant, Regulation (EU) 2026/…[+] and other Union law.

6. For integral combinations of a medicinal product with a medical device and for combinations of a medicinal product with a product other than a medical device, the marketing authorisation holder shall be responsible for the whole product in terms of compliance of the medicinal product with the requirements of this Directive and Regulation (EU) 2026/…[+].

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

7. The marketing authorisation holder shall be established in the Union.

8. Where the marketing authorisation holder considers, or has reason to believe, that the medicinal product it has made available on the market is not in compliance with the marketing authorisation or this Directive or Regulation (EU) 2026/…[+] it shall immediately:

   (a) take the corrective action necessary to bring the medicinal product into conformity, or to withdraw or recall it, as appropriate; and

   (b) inform the competent authorities of the Member States or the Agency, as applicable, and the distributors concerned to that effect.

9. Upon request, the marketing authorisation holder shall provide the competent authorities of the Member States or the Agency, as applicable, with free samples in sufficient quantities to enable controls to be carried out on the medicinal products that it has placed on the market.

10. Upon request, the marketing authorisation holder shall provide the competent authority of the Member State or the Agency, as applicable, with all data relating to the volume of sales of the medicinal product and any data in its possession relating to the volume of medical prescriptions for the medicinal product.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

Article 59

Specific requirements on the making available and supply of a medicinal product in a Member State

1. With a view to facilitating access to a medicinal product that is covered by a valid marketing authorisation within the territory of a Member State and that is subject to regulatory protection under Article 83 or, if applicable, market exclusivity in accordance with Article 73 of Regulation (EU) 2026/…[+], a Member State may request the marketing authorisation holder to place the medicinal product on the market of that Member State and to supply it so that the needs of patients in the Member State in question are met as specified by that Member State.

2. For the purposes of paragraph 1, a Member State may require the marketing authorisation holder to do one or more of the following:

   (a) submit a valid pricing and reimbursement application, in accordance with national law;

   (b) fulfil specific requirements for marketing authorisation holders in procurement procedures, in accordance with national and Union law;

   (c) establish a roll-out plan, in accordance with paragraph 3.

   The practical arrangements to implement the requirements referred to in this paragraph shall be proportionate to the objective pursued and in accordance with Union law.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

3. For the purposes of paragraph 2, point (c), the roll-out plan shall include information about the supply of the medicinal product by the marketing authorisation holder over a given period in the Member State concerned. The roll-out plan shall be prepared by the marketing authorisation holder and be agreed by the Member State concerned. The Member State may, where justified, require the marketing authorisation holder to update the roll-out plan.

4. Requests pursuant to paragraph 1, together with the practical arrangements referred to in paragraph 2, shall be communicated to the marketing authorisation holder, within one year of the granting of the marketing authorisation for the medicinal product concerned. The communication under this paragraph shall contain explicit reference to this Article.

For the purposes of implementing this Article, the Member State and the marketing authorisation holder shall cooperate in good faith and make best efforts to ensure, within the limits of their responsibility, the availability and supply of the medicinal product concerned.

5. Where, within three years of the date on which a Member State submitted its request pursuant to paragraph 2 of this Article, the marketing authorisation holder has not, within the limits of its responsibilities, made the medicinal product available and has not supplied it continuously within that period so that the needs of patients in the requesting Member State are met, the regulatory market protection for that medicinal product provided for in Article 83(2) of this Directive, and, if applicable, the extension of market exclusivity provided for in Article 74(1) of Regulation (EU) 2026/…[+] shall not apply within that Member State. In such cases, Article 169(5) of this Directive shall apply.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

6. The Member State shall make the information referred to in paragraph 5 publicly available without undue delay. For medicinal products authorised in accordance with Regulation (EU) 2026/…[+], the Member State shall also notify the Agency.

7. By way of derogation from Article 83(1), a marketing authorisation application may be validated and assessed by the competent authorities of the Member States or the Agency six years after the start of the regulatory data protection period of the reference medicinal product, where the medicinal product is a generic medicinal product or a biosimilar medicinal product and where a Member State has made information publicly available with regard to that reference medicinal product in accordance with paragraph 6.

Marketing authorisations validated and assessed in accordance with the first subparagraph shall not be granted prior to the expiry of the regulatory data protection period.

8. This Article shall not affect the application of national legislation or procedural rules, including with regard to pricing and reimbursement, public procurement or any other procedures, that aim at making available and supplying the medicinal product concerned within the territory of the Member States at any time following the granting of the marketing authorisation.

This Article shall also not affect the right of marketing authorisation holders to make available and supply the medicinal product concerned in a Member State by following the relevant procedures under national law, regardless of whether a request in accordance with paragraph 1 has been made by that Member State.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

9. Member States' representatives may request the Commission to discuss issues related to the practical application of this Article in the Committee established by Council Decision 75/320/EEC[50] ('Pharmaceutical Committee'). The Commission may invite bodies responsible for health technology assessments as referred to in Regulation (EU) 2021/2282 of the European Parliament and of the Council[51] or national bodies responsible for pricing and reimbursement, as required, to participate in the deliberations of the Pharmaceutical Committee.

The Pharmaceutical Committee may exchange views on national measures envisaged in the event that the obligations under this Article are not met.

10. Marketing authorisation holders shall comply with the obligations set out in this Article, except in exceptional and unforeseeable circumstances, such as those related to disruptions of supply, or in duly justified circumstances that are entirely outside the marketing authorisation holder's control, the consequences of which could not have been avoided even if all best and reasonable measures had been taken. In such cases the marketing authorisation holder shall provide an explanation of the case and circumstances and justify the reasons for non-compliance.

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50 Council Decision 75/320/EEC of 20 May 1975 setting up a pharmaceutical committee (OJ L 147, 9.6.1975, p. 23, ELI: http://data.europa.eu/eli/dec/1975/320/oj).

51 Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (OJ L 458, 22.12.2021, p. 1, ELI: http://data.europa.eu/eli/reg/2021/2282/oj).

Article 60

Responsibility to report public financial support

1. Marketing authorisation holders shall publicly declare any direct financial support received from any public authority, publicly funded body, philanthropic organisation or not-for-profit organisation or fund, in relation to any activities for the research and development of a medicinal product covered by a national or centralised marketing authorisation, irrespective of the legal entity that received that support.

2. Within 30 days of the granting of the marketing authorisation, the marketing authorisation holder shall:

   (a) draw up an electronic report listing:

      (i) the amount of financial support received and the date thereof;

      (ii) the entity that provided the financial support referred to in point (i);

      (iii) the legal entity that received the support referred to in point (i);

   (b) ensure that the electronic report is accurate and that it has been audited by an independent external auditor;

   (c) make the electronic report accessible to the public via a dedicated webpage;

   (d) communicate the electronic link to such webpage to the competent authority of the Member State or, where appropriate, to the Agency.

3. For the medicinal products authorised under this Directive, the competent authority of the Member State shall communicate in a timely manner the electronic link to the Agency.

4. Marketing authorisation holders shall keep the electronic link up to date and, as necessary, update the report annually.

5. The Member States shall take appropriate measures to ensure that paragraphs 1, 2 and 4 are complied with by the marketing authorisation holders established within their territory.

6. The Commission shall adopt implementing acts to lay down the principles and format for the information to be reported pursuant to paragraph 2, by … [18 months from the date of entry into force of this Directive]. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 217(2).

Article 61

Traceability of substances used in the manufacture of medicinal products

1. The marketing authorisation holder shall, when necessary, ensure the traceability of an active substance, starting material, excipient or any other substance intended or expected to be present in a medicinal product at all stages of manufacturing and distribution.

2. The marketing authorisation holder shall be able to identify any natural or legal person from whom it has been supplied with an active substance, starting material, excipient or any other substance intended or expected to be present in a medicinal product.

3. The marketing authorisation holder and its suppliers of an active substance, starting material, excipient or any other substance used in the manufacture of a medicinal product shall have in place systems and procedures that allow for the information referred to in paragraph 2 to be made available, upon request, to the competent authorities of the Member States or the Agency, as applicable.

4. The marketing authorisation holder and its suppliers shall have in place systems and procedures to identify the other natural or legal persons to whom an active substance, starting material, excipient or any other substance used in the manufacture of a medicinal product referred to in paragraph 2 have been supplied. This information shall, upon request, be made available to the competent authorities of the Member States or the Agency, as applicable.

Article 62

Placing on the market of products with paediatric indications

Where a medicinal product is authorised for a paediatric indication following completion of an agreed paediatric investigation plan and that medicinal product has already been marketed with other therapeutic indications, the marketing authorisation holder shall, within two years of the date on which the medicinal product is authorised for that paediatric indication, place the medicinal product on the market taking into account that paediatric indication in all Member States where the medicinal product is already placed on the market.

A register, coordinated by the Agency, and made publicly available, shall mention deadlines that apply pursuant to this Article.

Article 63

Discontinuation of the placing on the market of paediatric medicinal products

If a medicinal product is authorised for a paediatric indication and the marketing authorisation holder has benefited from rewards or incentives under Article 88 of this Directive or Article 95 of Regulation (EU) 2026/…[+], and those periods of protection have expired, and if the marketing authorisation holder intends to discontinue placing the medicinal product on the market, the marketing authorisation holder shall transfer the marketing authorisation to a third party or allow a third party, which has declared its intention to continue to place the medicinal product in question on the market, to use the pharmaceutical, non-clinical and clinical documentation contained in the file of the medicinal product on the basis of Article 15 of this Directive.

The marketing authorisation holder shall inform the competent authorities of the Member States or the Agency, as applicable, of its intention to discontinue the placing on the market of the medicinal product no less than twelve months before the discontinuation. The competent authorities of the Member States or the Agency, as applicable, shall make this fact publicly available.

Article 64

Liability of the marketing authorisation holder

The granting of a marketing authorisation shall not affect the civil and criminal liability of the marketing authorisation holder.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

Chapter VI
Product information

Article 65

Summary of product characteristics

1. The summary of product characteristics shall contain the particulars listed in Annex V.

2. For marketing authorisations under Articles 10 to 13 and subsequent variations of such marketing authorisations, if one or more of the therapeutic indications, posologies, pharmaceutical forms, methods or routes of administration or any other way in which the medicinal product may be used and that are part of the summary of product characteristics of the reference medicinal product are still covered by a patent or a supplementary protection certificate for medicinal products at the time when the generic, biosimilar, hybrid or bio-hybrid medicinal product is marketed, the applicant for a marketing authorisation or a variation of a marketing authorisation for a generic, biosimilar, hybrid or bio-hybrid medicinal product can request that such information not be included in its marketing authorisation. In such cases, however, all relevant safety information related to the safe use of the medicinal product shall be included in the summary of product characteristics.

Article 66

General principles for package leaflets

1. A package leaflet shall be mandatory for medicinal products. The package leaflet shall be made available by the marketing authorisation holder in the packaging in paper format and electronically in accordance with the specifications, standards and format specified by the implementing acts adopted pursuant to paragraph 6.

2. The package leaflet shall be written and designed in a clear and understandable way, enabling users to act appropriately, when necessary with the help of healthcare professionals.

3. By derogation from paragraph 1, Member States may decide, for specific categories of medicinal products or for all medicinal products, following a consultation of patients, healthcare professionals and other relevant stakeholders, that marketing authorisation holders are only required to make available an electronic version of the package leaflet.

   If a Member State decides that marketing authorisation holders are only required to make available an electronic version of the package leaflet:

   (a) the patient's right to a printed copy of the package leaflet shall be guaranteed upon request and free of charge;

   (b) it shall not preclude the marketing authorisation holder from providing the package leaflet in paper format in addition to the electronic version, on a voluntary basis.

It shall be ensured that the information in digital format is easily accessible to all patients. The marketing authorisation holder shall be responsible for preparing the electronic version of the package leaflet and ensuring that the electronic and printed versions of the package leaflet are made readily available to the patient.

4. The obligation to make available the package leaflet in paper format in the packaging in a Member State shall not constitute a reason justifying a refusal by the marketing authorisation holder to supply the medicinal product on the market in that Member State.

5. By derogation from paragraphs 1 and 2 of this Article, where the information required under Articles 67 and 76 appears on the outer packaging or on the immediate packaging, a package leaflet shall not be required.

6. The Commission shall by … [18 months from the date of entry into force of the Directive] adopt implementing acts to:

(a) establish common standards and formats for the electronic version of the package leaflet, the summary of product characteristics and the labelling, taking into account available technologies;

(b) establish criteria for the provision of the product information referred to in point (a) by the marketing authorisation holder through secure digital platforms and digital services and for the provision, establishment, management and accessibility of such digital platforms and services;

(c) establish the necessary procedures to validate the electronic version of the package leaflet and to make them available to patients;

(d) specify information on the packaging on how to access the electronic version of the package leaflet;

(e) specify the details on how to include the commonly recognised global antimicrobial resistance symbol as referred to in Article 72(2) in the section of the package leaflet that contains specific information about the medicinal product concerned and information on antimicrobial resistance and on the importance of appropriate use and disposal of antimicrobials.

Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 217(2).

7. The Agency shall make a system available to accommodate the electronic product information after consultation with Member States and the relevant stakeholders. The system shall be available by … [18 months from the date of entry into force of this Directive].

8. When accessing the package leaflet electronically, the protection of personal data shall be ensured. Any technology giving access to the information shall ensure the protection of personal data in accordance with Regulation (EU) 2016/679 and Directive 2002/58/EC and shall not allow the identification, profiling or tracking of individuals, nor shall it be used for commercial purposes, including for advertising or marketing activities.

Article 67

Content of package leaflet

1. The package leaflet shall be drawn up in accordance with the summary of product characteristics referred to in Article 65(1) and shall include the particulars listed in Annex VI.

2. The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use.

Article 68

Labelling on the outer or immediate packaging

1. Labelling particulars listed in Annex IV shall appear on the outer packaging of medicinal products or, where there is no outer packaging, the immediate packaging, with the exception of the packaging referred to in Article 69, paragraphs 2 and 3.

2. The Commission is empowered to adopt delegated acts in accordance with Article 218 to:

   (a) amend the list of labelling particulars set out in Annex IV in order to take account of scientific progress or patients' needs;

   (b) supplement Annex IV by setting out a reduced list of mandatory labelling particulars that shall appear on the outer packaging of multi-country packages that are also multilingual.

Article 69

Labelling on blister packs or small immediate packaging

1. The labelling particulars listed in Annex IV shall appear on immediate packaging other than immediate packaging referred to in paragraphs 2 and 3.

2. On immediate packaging that takes the form of blister packs and that is placed in an outer packaging that complies with the requirements laid down in Articles 68 and 76, at least the following particulars shall appear:

   (a) the name of the medicinal product;

   (b) the name of the marketing authorisation holder placing the product on the market;

   (c) the expiry date;

   (d) the batch number.

3. On small immediate packaging units on which the particulars laid down in Articles 68 and 76 cannot be displayed, at least the following particulars shall appear:

   (a) the name of the medicinal product and, if necessary, the route of administration;

   (b) the method of administration, if not already evident from the name of the medicinal product or from the route of administration of the medicinal product, as referred to in point (a);

(c) the expiry date;

(d) the batch number;

(e) the contents by weight, by volume or by unit.

Article 70

Safety features

1. Medicinal products subject to medical prescription shall bear the safety features referred to in point (p) of Annex IV unless they have been listed in accordance with paragraph 2, second subparagraph, point (b).

Medicinal products not subject to medical prescription shall not be required to bear the safety features referred to in point (p) of Annex IV unless they have been listed in accordance with paragraph 2, second subparagraph, point (b), or where the marketing authorisation holder chooses to so display those features.

2. The Commission shall adopt delegated acts in accordance with Article 218 to supplement Annex IV by laying down detailed rules for the safety features.

Those delegated acts shall set out:

(a) the characteristics and technical specifications of the unique identifier of the safety features referred to in point (p) (ii) of Annex IV that enables the authenticity of medicinal products to be verified and individual packs to be identified;

(b) the lists containing the medicinal products or product categories that, in the case of medicinal products subject to medical prescription shall not bear the safety features, and in the case of medicinal products not subject to medical prescription shall bear the safety features referred to in point (p) of Annex IV;

(c) the procedures for the notification to the Commission provided for in paragraph 4 and a rapid system for evaluating and deciding on such notification for the purpose of applying point (b);

(d) the modalities for the verification of the safety features referred to in point (p) of Annex IV by the manufacturers, wholesale distributors, pharmacists and other natural or legal persons authorised or entitled to supply medicinal products to the public and by the competent authorities of the Member States or the Agency, as applicable;

(e) provisions on the establishment, management and accessibility of a repositories system in which information on the safety features, enabling the verification of the authenticity and identification of medicinal products, as provided for in point (p) of Annex IV shall be contained.

In establishing the lists referred to in the second subparagraph, point (b), the Commission shall take into consideration the risk of falsification relating to the medicinal products or categories of medicinal products concerned. To this end, at least the following criteria shall be applied:

(a) the price and sales volume of the medicinal product;

(b) the number and frequency of previous cases of falsified medicinal products being reported within the Union and in third countries and the evolution of the number and frequency of such cases to date;

(c) the specific characteristics of the medicinal products concerned;

(d) the severity of the conditions intended to be treated;

(e) other potential risks to public health.

The modalities referred to in the second subparagraph, point (d), shall allow the verification of the authenticity of each supplied pack of the medicinal products bearing the safety features referred to in point (p) of Annex IV and determine the extent of such verification. When establishing those modalities, the particular characteristics of the supply chains in Member States, and the need to ensure that the impact of verification measures on particular actors in the supply chains is proportionate, shall be taken into account.

For the purposes of the second subparagraph, point (e), the costs of the repositories system shall be borne by the marketing authorisation holder or manufacturing authorisation holder of the medicinal product bearing the safety features, as relevant.

3. When adopting delegated acts referred to in paragraph 2, the Commission shall take due account of at least the following:

(a) the protection of personal data as provided for in Union law;

(b) the legitimate interests to protect information of a commercially confidential nature;

(c) the ownership and confidentiality of the data generated by the use of the safety features; and

(d) the cost-effectiveness of the measures.

4. The competent authorities of the Member States shall notify the Commission of medicinal products not subject to medical prescription that they consider to be at risk of falsification and may inform the Commission of medicinal products that they consider not to be at risk of falsification in accordance with the criteria set out in paragraph 2, third subparagraph.

5. Member States may, for the purposes of reimbursement or pharmacovigilance, extend the scope of application of the unique identifier of the safety features referred to in point (p) (ii) of Annex IV to any medicinal product subject to medical prescription or subject to reimbursement.

6. The competent authorities of the Member States or the Agency, as applicable, may, for the purposes of reimbursement, pharmacovigilance or pharmacoepidemiology or to monitor any potential, expected or actual shortage of a medicinal product, as well as to assess the general supply situation to avoid shortages, use the information contained in the repositories system referred to in paragraph 2, second subparagraph, point (e).

7. Member States may, for the purposes of patient safety, extend the scope of application of the anti-tampering device referred to in point (p) of Annex IV to any medicinal product.

Article 71

Labelling and instruction leaflet of radionuclides and radiopharmaceuticals

1. In addition to the rules laid down in this Chapter, the outer carton and the container of medicinal products containing radionuclides shall be labelled in accordance with the regulations for the safe transport of radioactive materials laid down by the International Atomic Energy Agency. Moreover, the labelling shall comply with the provisions set out in paragraphs 2 and 3.

2. The label on the shielding shall include the particulars laid down in Article 68. In addition, the label on the shielding shall explain in full, the codes used on the vial and shall indicate, where necessary, for a given time and date, the amount of radioactivity per dose or per vial and the number of capsules, or, for liquids, the number of millilitres in the container.

3. In addition to the requirements of Article 68, the vial shall be labelled with the following information:

   (a) the name of the medicinal product or code of the medicinal product, including the name or chemical symbol of the radionuclide;

   (b) the batch identification and expiry date;

(c) the international symbol for radioactivity;

(d) the name and address of the manufacturer;

(e) the amount of radioactivity as specified in paragraph 2.

4. The marketing authorisation holder shall ensure that a detailed instruction leaflet is enclosed with the packaging of radiopharmaceuticals, radionuclide generators, radionuclide kits or radionuclide precursors. The text of this leaflet shall be established in accordance with Article 67(1). In addition, the leaflet shall include any precautions to be taken by the user and the patient during the preparation and administration of the medicinal product and special precautions for the disposal of the packaging and its unused contents.

Article 72

Special information requirements for antimicrobials

1. The marketing authorisation holder shall ensure that educational material is available to healthcare professionals, including through medical sales representatives as referred to in Article 178(1), point (c), regarding the appropriate use of diagnostic tools, testing or other diagnostic approaches related to antimicrobial-resistant pathogens, that provides information on the use of the antimicrobial. Any such educational material shall be compatible and in accordance with the summary of product characteristics.

2. The marketing authorisation holder shall include a section in the beginning of the package leaflet of antimicrobials that contains the global antimicrobial resistance symbol, specific information about the medicinal product concerned and information on antimicrobial resistance and on the importance of the appropriate use and disposal of antimicrobials.

Where a Member State decides, in accordance with Article 66(3), first subparagraph, that marketing authorisation holders are only required to make available an electronic version of the package leaflet, the information referred to in the first subparagraph of this paragraph is made available to patients also in paper format ('awareness card'). The awareness card shall be presented in a distinct and immediately visible way. However, in duly justified cases referred to in Article 78, a Member State may decide to exempt marketing authorisation holders from the obligation to make the awareness card available to patients in paper format.

3. The text of the information referred to in paragraph 2 shall be aligned with Annex VI.

Article 73

Legibility

The package leaflet, labelling particulars and the awareness card referred to in this Chapter shall be easily legible and comprehensible, and indelible.

Article 74

Accessibility for persons with disabilities

The name of the medicinal product, followed by its strength, if appropriate, and pharmaceutical form, if appropriate, shall also be expressed in Braille format on the outer packaging. The marketing authorisation holder shall ensure that the package leaflet referred to in Article 66 is made available free of charge upon request from patients' organisations in formats appropriate for persons with disabilities, including blind and partially-sighted persons.

Article 75

Member States labelling requirements

1. Notwithstanding Article 81, Member States may require the use of certain forms of labelling of the medicinal product making it possible to ascertain:

   (a) the price of the medicinal product;

   (b) the reimbursement conditions;

   (c) the prescription status of the medicinal product, in accordance with Chapter IV;

   (d) authenticity and identification of medicinal products in accordance with Article 70(5) and (7).

   (e) the identity of the medicinal product in accordance with national requirements, including for statistical reasons.

2. For medicinal products for which a centralised marketing authorisation as referred to in Article 6 has been granted, Member States shall, when applying this Article, consider the detailed guidance published pursuant to Article 80.

Article 76

Symbols and pictograms

The outer packaging or, where there is no outer packaging, the immediate packaging, and the package leaflet may include symbols or pictograms designed to clarify certain particulars or information set out in Article 67(1), and Articles 68 and 72 and other information compatible with the summary of product characteristics that is useful for the patient, to the exclusion of any element of a promotional nature.

Article 77

Requirements on languages

1. The package leaflet and labelling particulars referred to in Article 67(1) and in Article 68(1) shall appear in one or more official languages of the Member State where the medicinal product is placed on the market, as specified by that Member State for the purposes of this Directive.

   The electronic version of the package leaflet shall also appear in the English language.

2. Paragraph 1 shall not prevent the package leaflet and labelling particulars from appearing in several languages, provided that the same particulars appear in all the languages used.

3. The awareness card referred to in Article 72(2) shall appear in one or more official languages of the Member State where the medicinal product is placed on the market, as specified by that Member State for the purposes of this Directive.

4. A Member State may grant a full or partial exemption from the obligation that the package leaflet, the labelling particulars and the awareness card be in one or more official languages of the Member State where the medicinal product is placed on the market, as specified by that Member State for the purposes of this Directive.

5. By way of derogation from paragraph 1, 3 or 4, in the case of multi-language packages or multi-country packages that are also multilingual, Member States may allow that the package leaflet, the labelling particulars and the awareness card only be in an official language of the Union that is commonly understood in the Member States where the multi-language package or multi-country package that is also multilingual is marketed.

Article 78

Member States exemptions from requirements for labelling and package leaflet

The competent authorities of the Member States may, subject to measures they consider necessary to safeguard public health, grant an exemption to the obligation that the particulars required pursuant to Articles 67, 68 and 69 are to appear in the labelling and in the package leaflet in the following cases:

(a) where the medicinal product is not intended to be delivered directly to the patient;

(b) where there are problems in respect of the availability of the medicinal product;

(c) where there are space constraints due to the size of the packaging or of the package leaflet or in the case of multi-language or multi-country packages or package leaflets;

(d) in the context of a public health emergency;

(e) to facilitate access to medicines in Member States.

Article 79

Approval of the labelling and package leaflet

1. One or more mock-ups of the outer packaging and the immediate packaging of a medicinal product, together with the package leaflet, shall be submitted to the competent authorities of the Member States or the Agency, as applicable, when the marketing authorisation application is submitted. The results of assessments carried out in cooperation with target patient groups shall also be provided to the competent authorities of the Member States or to the Agency, as applicable.

2. The competent authorities shall refuse the marketing authorisation if the labelling or the package leaflet does not comply with this Chapter or if it is not in accordance with the particulars listed in the summary of product characteristics.

3. Any proposed change to an aspect of the labelling or the package leaflet covered by this Chapter that is not connected with the summary of product characteristics shall be submitted to the competent authorities of the Member States or the Agency, as applicable. If the competent authorities of the Member States or the Agency, as applicable, have not opposed a proposed change within 90 days of the submission of the request, the applicant may put the change into effect.

4. The fact that the competent authorities do not refuse a marketing authorisation pursuant to paragraph 2 or a change to the labelling or the package leaflet pursuant to paragraph 3 does not alter the general legal liability of the manufacturer and the marketing authorisation holder.

Article 80

Guidance on labelling particulars

In consultation with the Member States and the parties concerned, the Commission shall draw up and publish detailed guidance concerning in particular:

(a) the wording of certain special warnings for certain categories of medicinal products;

(b) the wording on prudent use of antimicrobials;

(c) the particular information needs relating to medicinal products not subject to medical prescription;

(d) the legibility of labelling particulars and particulars in the package leaflet;

(e) the methods for the identification and authentication of medicinal products;

(f) the information for specific excipients that feature in the labelling of medicinal products;

(g) harmonised provisions for the implementation of Article 75;

(h) use of symbols, pictograms and abbreviations.

Article 81

Placing on the market of labelled medicinal products

Member States may not prohibit or impede the placing on the market of medicinal products within their territory on grounds connected with labelling or the package leaflet where these comply with the requirements of this Chapter.

Article 82

Non-compliance with the requirements for labelling and package leaflet

Where the provisions of this Chapter are not complied with, and a notice served on the marketing authorisation holder concerned has remained without effect, the competent authorities of the Member States may suspend the marketing authorisation, until the labelling and the package leaflet of the medicinal product in question have been made to comply with this Chapter.

Chapter VII

Regulatory data protection and regulatory market protection, unmet medical need and rewards for paediatric medicinal products

Article 83

Regulatory data protection and regulatory market protection

1. Where a marketing authorisation has been granted for a medicinal product in accordance with Article 7(2) of this Directive, the data referred to in Annex I that were submitted with a view to obtaining that marketing authorisation shall not be referred to by another marketing authorisation applicant for a subsequent marketing authorisation for a period of eight years from the date when the marketing authorisation for that medicinal product was granted, or nine years from that date in cases where one additional year of data protection is granted in accordance with Article 41(1) of Regulation (EU) 2026/…[+] ('regulatory data protection period'). For marketing authorisations that belong to the same global marketing authorisation in accordance with Article 6(2) of this Directive, the regulatory data protection period shall start from the date when the initial marketing authorisation was granted in the Union.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

2. A medicinal product covered by a subsequent marketing authorisation referred to in paragraph 1 shall not be placed on the market for a period of one year after the expiry of regulatory data protection period (‘regulatory market protection period’). The regulatory market protection period may be extended in accordance with Article 84.

3. By way of derogation from paragraph 1, the marketing authorisation holder concerned may grant the marketing authorisation applicant for another marketing authorisation access to its data submitted in accordance with Annex I by means of a letter of access in accordance with Article 15.

4. By way of derogation from paragraphs 1 and 2, when a compulsory licence has been granted by a relevant authority in the Union pursuant to Regulation (EU) 2025/2645 or to national compulsory licensing frameworks, the regulatory data protection and regulatory market protection with regard to that licensee shall be suspended to the extent required by the compulsory licence and for the duration and territory of the Member States for which the compulsory licence has been granted.

5. The regulatory data protection period shall also apply in Member States where the medicinal product is not authorised or is no longer authorised.

6. The competent authorities of the Member States shall make available on their website the list of medicinal products for which they have granted a national marketing authorisation and that are protected by regulatory data protection and regulatory market protection, indicating the applicable extension in accordance with Article 84. The Agency shall compile and publish a list of hyperlinks to the websites referred to in this paragraph.

Article 84

Additional regulatory market protection periods

1. The regulatory market protection period referred to in Article 83(2) shall be extended by 12 months:

   (a) where, at the time of the initial marketing authorisation application, the marketing authorisation applicant demonstrates that the medicinal product addresses an unmet medical need as referred to in Article 85; or

   (b) for medicinal products containing a new active substance, where the marketing authorisation applicant demonstrates that:

      (i) the clinical trials supporting the initial marketing authorisation application use a relevant and evidence-based comparator in accordance with the scientific advice provided by the Agency; and

      (ii) the marketing authorisation application has been submitted first to the competent authority in the Union or has been submitted no later than 90 days of the submission of the application for the first marketing authorisation outside the Union; or

(c) for medicinal products containing a new active substance, where the marketing authorisation applicant demonstrates that:

(i) the clinical trials supporting the initial marketing authorisation application use a relevant and evidence-based comparator in accordance with the scientific advice provided by the Agency; and

(ii) clinical trials evaluating the efficacy of the medicinal product and used for the marketing authorisation were conducted in more than one Member State; or

(d) for medicinal products containing a new active substance, where the marketing authorisation applicant justifies that a clinical trial as referred to in points (b)(i) and (c)(i) is not possible or appropriate and demonstrates that:

(i) clinical trials evaluating the efficacy of the medicinal product and used for the marketing authorisation were conducted in more than one Member State; and

(ii) the marketing authorisation application has been submitted first to the competent authority in the Union or has been submitted no later than 90 days of the submission of the application for the first marketing authorisation outside the Union.

In the case of a conditional marketing authorisation granted in accordance with Article 20 of Regulation (EU) 2026/…[+], the extension referred to in the first subparagraph, point (a), shall only apply if:

– within four years of the granting of the conditional marketing authorisation, the medicinal product has been granted a marketing authorisation in accordance with Article 20(7) of Regulation (EU) 2026/…[+]; and

– in the case of medicinal products referred to in Article 85(1), point (b), of this Directive, the studies referred to in Article 20(4) of Regulation (EU) 2026/…[+] include clinical trials that use, where possible and appropriate, a relevant and evidence-based comparator.

2. The regulatory market protection period shall be extended by an additional year if, during the regulatory data protection period referred to in Article 83(1), the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation and based on supporting data submitted by the marketing authorisation holder, are held to bring a significant clinical benefit in comparison with existing therapies. This extension may only be granted once.

3. The cumulative duration of the regulatory market protection for a medicinal product shall not exceed two years from the date when the regulatory data protection expires, except when one additional year of the regulatory market protection is granted in accordance with paragraph 2.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

4. The Agency shall set scientific guidelines on criteria for proposing a relevant and evidence-based comparator for clinical trials, as referred to in paragraph 1, points (b)(i) and (c)(i), taking into account the results of the consultation of the Commission and the authorities or bodies involved in the consultation process referred to in Article 169 of Regulation (EU) 2026/…[+].

Article 85

Medicinal products addressing an unmet medical need

1. A medicinal product shall be considered as addressing an unmet medical need if at least one of its therapeutic indications relates to a life threatening or severely debilitating disease and either of the following conditions are met:

   (a) there is no medicinal product authorised in the Union for such disease;

   (b) the use of that medicinal product for such a disease results in clinically relevant improvement in efficacy, or in safety with at least comparable efficacy, in comparison with existing medicinal products or other methods of prevention, diagnosis or treatment authorised in the Union.

2. Designated orphan medicinal products referred to in Article 69 of Regulation (EU) 2026/…[+] shall be considered as addressing an unmet medical need.

3. The Agency shall adopt scientific guidelines to support the application of this Article. To this end, it shall consult the Commission and the authorities or bodies involved in the consultation process referred to in Article 169 of Regulation (EU) 2026/…[+].

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

Article 86

Regulatory data protection for repurposed medicinal products

1. A regulatory data protection period of four years shall be granted for a medicinal product with respect to a new therapeutic indication not previously authorised in the Union for the active substance(s), provided that:

   (a) adequate clinical studies and, where relevant, non-clinical studies or tests were carried out in relation to the new therapeutic indication demonstrating that it is of significant clinical benefit; and

   (b) the medicinal product is authorised in accordance with Articles 10 to 13 and has not previously benefitted from regulatory data protection or 25 years have passed since the granting of the initial marketing authorisation for the medicinal product concerned.

2. The regulatory data protection period referred to in paragraph 1 may only be granted once for any given medicinal product.

3. During the regulatory data protection period referred to in paragraph 1, the marketing authorisation shall indicate that the medicinal product is an existing medicinal product authorised in the Union that has been authorised with an additional therapeutic indication.

Article 87

Exception relating to intellectual property rights

1. The protection provided by patent rights or supplementary protection certificates for medicinal products shall not be regarded as infringed when the necessary studies, trials and other activities are conducted for the purposes of:

(a) obtaining marketing authorisations, in particular for generic, biosimilar, hybrid or bio-hybrid medicinal products and for subsequent variations;

(b) conducting health technology assessments as defined in Article 2, point (5), of Regulation (EU) 2021/2282;

(c) obtaining pricing and reimbursement approvals;

(d) complying with subsequent practical requirements associated with activities referred to in points (a), (b) and (c);

(e) submitting an application on procurement tenders, in compliance with Union and national law, to the extent that it does not entail the sale or offering for sale or marketing of the medicinal product concerned during the protection period provided by patent rights or supplementary protection certificates.

The activities conducted exclusively for the purposes set out in the first subparagraph may cover, where relevant, the submission of a marketing authorisation application and the offer, manufacture, sale, supply, storage, import, use and purchase of medicinal products or processes, including by third party suppliers and service providers.

2. Decisions adopted concerning the activities referred to in paragraph 1 shall not be considered as infringing intellectual property rights, within the meaning of that paragraph. The intellectual property rights on the reference medicinal product shall not represent a valid ground to refuse, revoke or suspend decisions adopted concerning the activities referred to in paragraph 1.

3. The exception provided for in this Article shall not cover the placing on the market of the medicinal products resulting from such activities.

Article 88

Rewards for paediatric medicinal products

1. Where a marketing authorisation application includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the holder of the patent or supplementary protection certificate shall be entitled to a six-month extension of the period referred to in Article 13(1) and (2) of Regulation (EC) No 469/2009.

The first subparagraph shall also apply where completion of the agreed paediatric investigation plan fails to lead to the authorisation of a paediatric indication, but the results of the studies conducted are reflected in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.

2. The inclusion in a marketing authorisation of the statement referred to in Article 52(2) of this Directive or in Article 92(2) of Regulation (EU) 2026/…[+] shall be used for the purposes of applying paragraph 1.

3. Where the procedures laid down in Chapter III, Sections 3 and 4, have been used, the six-month extension of the period referred to in paragraph 1 shall be granted only if the medicinal product is authorised in all Member States.

4. In the case of an application for new therapeutic indications, which leads to the authorisation of a new paediatric indication for a medicinal product which is protected either by a supplementary protection certificate under Regulation (EC) No 469/2009, or by a patent which qualifies for the granting of a supplementary protection certificate, paragraphs 1, 2 and 3 shall not apply if the applicant applies for, and obtains, a one-year extension of the market protection period for the medicinal product concerned, on the grounds that this new paediatric indication brings a significant clinical benefit in comparison with existing therapies, in accordance with Article 84(2).

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

Chapter VIII

Post-marketing authorisation measures

Article 89

Imposed post-authorisation studies

1. After the granting of a national marketing authorisation, the competent authority of the Member State may impose an obligation on the marketing authorisation holder:

   (a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the competent authority of the Member State shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study;

   (b) to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the delegated acts adopted pursuant to Article 90 while taking into account the scientific guidance referred to in Article 127;

   (c) to conduct any other post-authorisation studies to improve the safe and effective use of the medicinal product, including treatment optimisation based on clinical experience;

(d) to conduct a post-authorisation ERA study or to collect monitoring data or information on use, if there are concerns about the risks to the environment or public health, including antimicrobial resistance, due to an authorised medicinal product, or other medicinal products containing the same active substance.

If the same concerns apply to more than one medicinal product, and post-authorisation studies are considered necessary, the competent authority of the Member State shall, following consultation with the Agency, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation ERA study.

The imposition of an obligation as referred to in this paragraph shall be duly justified, notified in writing, and shall include the objectives and timeframe for submission and conduct of the study.

2. The competent authority of the Member State shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of an obligation in accordance with paragraph 1 within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.

3. On the basis of the written observations presented by the marketing authorisation holder, the competent authority of the Member State shall withdraw or confirm the obligation imposed in accordance with paragraph 1. Where the competent authority of the Member State confirms the obligation, the national marketing authorisation shall be varied to include the obligation as a condition of the national marketing authorisation and, where appropriate, the risk management system shall be updated accordingly.

Article 90

Delegated acts on post-authorisation efficacy studies

In order to determine the situations in which post-authorisation efficacy studies may be required under Articles 47 and 89, the Commission is empowered to adopt delegated acts in accordance with Article 218, to specify measures supplementing the provisions in Articles 47 and 89.

Article 91

Recording of conditions related to national marketing authorisations

The marketing authorisation holder shall incorporate any safety or efficacy conditions referred to in Article 47(1), points (a) to (g) and (i), Article 48 and Article 89(1), points (a), (b) and (c), in the risk management system.

Article 92

Update of marketing authorisation related to scientific and technological developments

1. After a national marketing authorisation has been granted in accordance with Chapter III, the marketing authorisation holder shall, in respect of the methods of manufacture and control stated in the application for that marketing authorisation, take account of scientific and technical progress and introduce, by means of a variation, any changes that may be required to enable the medicinal product to be manufactured and controlled by means of generally accepted scientific methods.

Those changes shall be subject to the approval of the competent authority of the Member State.

2. The marketing authorisation holder shall without undue delay provide the competent authority of the Member State with any new information that might entail the amendment of the particulars or documents referred to in Articles 7 and 10 to 14, Article 44(5), Article 65, Annex I or Annex II.

In particular, the marketing authorisation holder shall without undue delay inform the competent authority of the Member State of any prohibition or restriction imposed on the marketing authorisation holder or any entity in contractual relationship with the marketing authorisation holder by the competent authorities of any country in which the medicinal product is marketed and of any other new information that might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all therapeutic indications and populations, whether or not included in the national marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.

3. The marketing authorisation holder shall ensure that the terms of the national marketing authorisation including the summary of product characteristics, the labelling and the package leaflet are kept up to date with current scientific knowledge, including the conclusions of the assessment and recommendations made publicly available by means of the European medicines web portal set up in accordance with Article 106 of Regulation (EU) 2026/…[+].

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

4. The competent authority of the Member State may at any time request the marketing authorisation holder to submit data demonstrating that the benefit-risk balance remains favourable. The marketing authorisation holder shall answer fully and within the time limit set any such request. The marketing authorisation holder shall also respond fully and within the time limit set to any request of the competent authority of the Member State regarding the implementation of any measures previously imposed, including risk minimisation measures.

5. The competent authority of the Member State may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The marketing authorisation holder shall submit that copy at the latest seven days after receipt of the request.

6. The marketing authorisation holder shall also respond fully and within the time limit set to any request of the competent authority of the Member State regarding the implementation of any measures previously imposed with regard to risks to the environment or public health, including antimicrobial resistance.

Article 93

Update of risk management plans

1. The holder of a national marketing authorisation for a medicinal product referred to in Articles 10 and 12, who did not submit a risk management plan in accordance with Article 22 shall submit to the competent authorities of the Member States concerned a risk management plan and a summary thereof, where the marketing authorisation for the reference medicinal product is withdrawn but the marketing authorisation for the medicinal product referred to in Articles 10 and 12 is maintained.

   The risk management plan and the summary thereof shall be submitted to the competent authorities of the Member States concerned within 60 days of the withdrawal of the marketing authorisation for the reference medicinal product by means of a variation.

2. The competent authority of the Member State may impose an obligation on the holder of a national marketing authorisation for a medicinal product referred to in Articles 10 and 12 to submit a risk management plan and summary thereof where:

   (a) additional risk minimisation measures have been imposed concerning the reference medicinal product; or

   (b) it is justified on pharmacovigilance grounds.

3. In the cases referred to in paragraph 1 and paragraph 2, point (a), the risk management plan shall be aligned with the risk management plan for the reference medicinal product.

4. The imposition of the obligation referred to in paragraph 2 shall be duly justified in writing, notified to the marketing authorisation holder and shall include the deadline for submission of the risk management plan and the summary thereof by means of a variation.

Article 94

Variation of national marketing authorisations

1. An application for a variation of a national marketing authorisation by the marketing authorisation holder shall be made electronically in the formats made available by the Agency, unless the variation is an update by the marketing authorisation holder of their information held in a database.

2. Variations shall be classified in different categories depending on the level of risk to public health and the potential impact on the quality, safety and efficacy of the medicinal product concerned. Those categories shall range from changes to terms of the national marketing authorisation that have the highest potential impact on the quality, safety or efficacy of the medicinal product, to changes that have no or minimal impact thereon and to administrative changes.

3. The procedures for examination of applications for variations shall be proportionate to the risk and impact involved. Those procedures shall range from procedures that allow implementation only after approval based on a complete scientific assessment to procedures that allow immediate implementation and subsequent notification by the marketing authorisation holder to the competent authority of the Member State. Such procedures may also include updates by the marketing authorisation holder of their information held in a database.

4. The Commission is empowered to adopt delegated acts in accordance with Article 218 to supplement this Directive by establishing the following:

(a) the categories referred to in paragraph 2 in which variations shall be classified;

(b) rules for the examination of applications for variations of the terms of national marketing authorisations, including procedures for updates through a database;

(c) the conditions for submission of a single application for more than one change to the terms of the same national marketing authorisation and for the same change to the terms of several national marketing authorisations;

(d) specifying exemptions from the variation procedures where the update of information in the national marketing authorisation referred to in Annex I may be directly implemented;

(e) the conditions and procedures for cooperation with competent authorities of third countries or international organisations on examination of applications for variations of the terms of national marketing authorisations.

Article 95

Variation of marketing authorisations
under the decentralised or mutual recognition procedure

1. Any application by the marketing authorisation holder to vary a marketing authorisation that has been granted in accordance with the Chapter III, Sections 3 and 4, shall be submitted to all the Member States that have previously authorised the medicinal product concerned under the procedure set out in Article 37 or 39. The same shall apply where the initial marketing authorisations were granted through separate procedures.

2. In the case of arbitration submitted to the Commission, the procedure laid down in Articles 44 and 45 shall apply by analogy to variations made to marketing authorisations.

Article 96

Variation based on additional evidence

The competent authority of the Member State may consider and after having informed the marketing authorisation holder decide upon additional evidence available, independently from the data submitted by the marketing authorisation holder. On that basis, if the additional evidence has an impact on the benefit-risk balance of a medicinal product, the competent authority of the Member State may recommend that the summary of product characteristics is updated. In this case the marketing authorisation holder shall submit to the competent authority of the Member State an appropriate application for a variation, including an updated summary of product characteristics. For medicinal products authorised in accordance with Article 37 or 39, the reference Member State and all Member States concerned shall be involved.

Article 97

Variation based on paediatric studies

1. On the basis of relevant paediatric studies received in accordance with Article 45(1) of Regulation (EC) No 1901/2006 of the European Parliament and of the Council[52], the competent authorities of the Member States may, following a consultation of the marketing authorisation holder, vary the national marketing authorisation for the medicinal product concerned accordingly and consequently the marketing authorisation holder shall update the summary of product characteristics and package leaflet of the medicinal product concerned.

2. The activities pursuant to paragraph 1 shall be concluded by … [seven years from the date of entry into force of this Directive].

3. When a medicinal product has been authorised under Chapter III, on the basis of the information received in accordance with Article 93 of Regulation (EU) 2026/…[+], the competent authorities of the Member States may vary the marketing authorisation of the medicinal product concerned accordingly and consequently the marketing authorisation holder shall update the summary of product characteristics and package leaflet of the medicinal product concerned.

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[52] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 378, 27.12.2006, p. 1, ELI: http://data.europa.eu/eli/reg/2006/1901/oj).

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

4. The Member States shall exchange information regarding the paediatric studies submitted and, as appropriate, their implications for any national marketing authorisations concerned.

5. The Agency shall coordinate the exchange of information under this Article.

Article 98

Union interest referral

1. The Member States or the Commission shall, in specific cases where the interests of the Union are involved, refer the matter to the Committee for Medicinal Products for Human Use under the procedure laid down in Articles 44 and 45 before any decision is reached on an application for a marketing authorisation or on the suspension or revocation of a marketing authorisation, or on any variation of the marketing authorisation that appears necessary. The Member States and the Commission shall consider any requests by the applicant or the marketing authorisation holder to make such a referral.

   Where the referral results from the evaluation of data relating to pharmacovigilance of an authorised medicinal product, the matter shall be referred to the Pharmacovigilance Risk Assessment Committee and Article 119(2) may apply. The Pharmacovigilance Risk Assessment Committee shall issue a recommendation in accordance with the procedure laid down in Article 44. The final recommendation shall be forwarded to the Committee for Medicinal Products for Human Use or to the coordination group, as appropriate, and the procedure laid down in Article 120 shall apply.

However, where one of the criteria listed in Article 118(1) is met, the procedure laid down in Articles 118, 119 and 120 shall apply.

The Member State concerned or the Commission shall clearly identify the question that is referred to the Committee for Medicinal Products for Human Use or to the Pharmacovigilance Risk Assessment Committee for consideration and shall inform the applicant or the marketing authorisation holder.

The Member States and the applicant or the marketing authorisation holder shall supply the Committee for Medicinal Products for Human Use or the Pharmacovigilance Risk Assessment Committee with all available information relating to the matter in question.

2. Where the referral to the Committee for Medicinal Products for Human Use or to the Pharmacovigilance Risk Assessment Committee concerns a range of medicinal products or a therapeutic class, the Agency may limit the procedure to certain specific parts of the marketing authorisation. In that event, Article 95 shall apply to those medicinal products only if they were covered by the marketing authorisation procedures referred to in Chapter III, Sections 3 and 4.

Where the scope of the procedure initiated under this Article concerns a range of medicinal products or a therapeutic class, medicinal products that are covered by a centralised marketing authorisation and that belong to that range or therapeutic class shall also be included in the procedure.

3. Without prejudice to paragraph 1, a Member State may, where urgent action is necessary to protect public health, at any stage of the procedure, suspend the marketing authorisation and prohibit the use of the medicinal product concerned on its territory until a definitive decision is adopted. It shall inform the Commission, the Agency and the other Member States, no later than the following working day, of the reasons for its action.

4. Where the scope of the procedure initiated under this Article, as determined in accordance with paragraph 2, includes medicinal products covered by a centralised marketing authorisation, the Commission may, where urgent action is necessary to protect public health, at any stage of the procedure, suspend the marketing authorisation and prohibit the use of the medicinal products concerned or take risk minimisation measures, until a definitive decision is adopted. The Commission shall inform the Agency and the Member States no later than the following working day of the reasons for its action.

Chapter IX
Pharmacovigilance

SECTION 1
GENERAL PROVISIONS

Article 99

Member State pharmacovigilance systems

1. Member States shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and their participation in Union pharmacovigilance activities.

   The Member State pharmacovigilance systems shall be used to collect information on the risks of medicinal products as regards patients' or public health. That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure.

2. Member States shall, by means of their pharmacovigilance system, evaluate all information scientifically, consider options for risk minimisation and prevention and take regulatory action concerning marketing authorisations as necessary. They shall perform a regular audit of their pharmacovigilance system and take corrective actions if necessary.

3. Each Member State shall designate a competent authority for the performance of pharmacovigilance tasks.

4. The Commission may request the Member States to participate, under the coordination of the Agency, in international harmonisation and standardisation of technical measures in relation to pharmacovigilance.

Article 100

Member State responsibilities regarding pharmacovigilance activities

1. The Member States shall:

(a) take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected adverse reactions to the competent authority of the Member State and involve, where appropriate, organisations representing consumers, patients and healthcare professionals in those tasks;

(b) facilitate patient reporting through the provision of alternative reporting formats in addition to web-based formats;

(c) take all appropriate measures to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports;

(d) ensure that the public is given important information on pharmacovigilance concerns relating to the use of a medicinal product in a timely manner through publication on the web portal and through other means of publicly available information as necessary;

(e) ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory that is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, and the batch number.

2. For the purposes of paragraph 1, points (a) and (e), the Member States may impose specific obligations on doctors, pharmacists and other healthcare professionals.

Article 101

Member State delegation of pharmacovigilance tasks

1. A Member State may delegate any of the tasks entrusted to it under this Chapter to another Member State subject to a written agreement of the latter. Each Member State may represent no more than one other Member State.

2. The delegating Member State shall inform the Commission, the Agency and all other Member States of the delegation in writing. The delegating Member State and the Agency shall make that information publicly available.

Article 102

Marketing authorisation holder pharmacovigilance system

1. Marketing authorisation holders shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks that is equivalent to the relevant Member State's pharmacovigilance system referred to in Article 99(1).

2. Marketing authorisation holders shall, by means of their pharmacovigilance system, evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary.

3. Marketing authorisation holders shall perform a regular audit of their pharmacovigilance system. They shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed.

4. As part of their pharmacovigilance system, marketing authorisation holders shall:

   (a) have permanently and continuously at their disposal an appropriately qualified person responsible for pharmacovigilance;

   (b) maintain and make available on request by the competent authority of a Member State or the Agency, as applicable, a pharmacovigilance system master file;

   (c) operate a risk management system for each medicinal product;

(d) monitor the outcome of risk minimisation measures that are contained in the risk management plan or that are laid down as conditions of the marketing authorisation pursuant to Article 47(1), points (a) to (g) and (i), and Article 48 and any obligations imposed in accordance with Article 89(1) points (a), (b) and (c);

(e) update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products.

5. The qualified person referred to in paragraph 4, point (a), shall reside and operate in the Union and shall be responsible for the establishment and maintenance of the marketing authorisation holder pharmacovigilance system. The marketing authorisation holder shall submit the name and contact details of the qualified person to the competent authority of the Member State and the Agency.

6. The marketing authorisation holder shall, upon request from the competent authority of the Member State or the Agency, as applicable, nominate a contact person for pharmacovigilance issues in that Member State who shall report to the qualified person referred to in paragraph 4, point (a).

7. To ensure patient safety, marketing authorisation holders shall have procedures in place to ensure continued fulfilment of their pharmacovigilance tasks for an appropriate period after the marketing authorisation has been withdrawn or revoked. The period shall be approved by the competent authority of the Member State or the Agency, as applicable, prior to the withdrawal or revocation of the marketing authorisation.

Article 103

Risk management system

1. Without prejudice to paragraphs 2, 3 and 4 of this Article, holders of national marketing authorisations granted before 21 July 2012 shall, by way of derogation from Article 102(4), point (c), not be required to operate a risk management system for the medicinal product covered by those national marketing authorisations.

2. The competent authority of a Member State may impose an obligation on the holder of a national marketing authorisation to operate a risk management system, as referred to in Article 102(4), point (c), if there are concerns about the risks affecting the benefit-risk balance of an authorised medicinal product. In that context, the competent authority of a Member State shall also oblige the holder of a national marketing authorisation to submit a risk management plan for the risk management system that they intend to introduce for the medicinal product concerned.

3. The obligation referred to in paragraph 2 shall be duly justified, notified in writing, and shall include the timeframe for submission of the risk management plan.

4. The competent authority of a Member State shall provide the holder of a national marketing authorisation with an opportunity to submit written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.

5. On the basis of the written observations submitted by the holder of a national marketing authorisation, the competent authority of a Member State shall withdraw or confirm the obligation referred to in paragraph 2. Where the competent authority of a Member State confirms that obligation, the marketing authorisation shall be varied accordingly to include that obligation and the measures to be taken as part of the risk management system as conditions of the national marketing authorisation referred to in Article 47(1), point (a).

Article 104

Funds for pharmacovigilance activities

1. The management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance shall be under the permanent control of the competent authorities of the Member States in order to guarantee their independence in the performance of those pharmacovigilance activities.

2. Paragraph 1 shall not preclude the competent authorities of the Member States from charging fees to marketing authorisation holders for performing pharmacovigilance activities on the condition that independence in the performance of those pharmacovigilance activities is strictly guaranteed.

SECTION 2

TRANSPARENCY AND COMMUNICATIONS

Article 105

National medicines web portal

1. Each Member State shall set up and maintain a national medicines web portal which shall be linked to the European medicines web portal established in accordance with Article 106 of Regulation (EU) 2026/…[+]. By means of the national medicines web-portals, the Member States shall make publicly available at least the following:

   (a) public assessment reports, together with a summary thereof;

   (b) summaries of product characteristics and package leaflets;

   (c) summaries of risk management plans for medicinal products covered by a national marketing authorisation in accordance with Chapter III;

   (d) information on the different ways of reporting suspected adverse reactions to medicinal products to competent authorities of the Member States by healthcare professionals and patients, including the standard web-based structured forms referred to in Article 104 of Regulation (EU) 2026/…[+];

   (e) information on prescription status of medicinal products authorised in their territory;

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(f) information on the shortage status of medicinal products as referred to in Article 125(1), point (c), and Article 126 of Regulation (EU) 2026/…[+].

2. The summaries referred to in paragraph 1, point (c), shall include, where relevant, a description of additional risk minimisation measures.

Article 106

Publication of assessments

The Agency shall make the final assessments, conclusions, recommendations, opinions and decisions referred to in Articles 111 to 120 publicly available by means of the European medicines web portal.

Article 107

Public announcements

1. As soon as the marketing authorisation holder intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product, and in any event at the same time or before the public announcement is made, it shall be required to inform the competent authorities of the Member States, the Agency and the Commission.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

2. The marketing authorisation holder shall ensure that information to the public is presented objectively and is not misleading.

3. Unless urgent public announcements are required for the protection of public health, the Member States, the Agency and the Commission shall inform each other not less than 24 hours prior to a public announcement relating to information on pharmacovigilance concerns.

4. For active substances contained in medicinal products authorised in more than one Member State, the Agency shall be responsible for the coordination between competent authorities of the Member States of safety announcements and shall provide timetables for the information being made publicly available.

5. Under the coordination of the Agency, the Member States shall make all reasonable efforts to agree on a common message in relation to the safety of the medicinal product concerned and the timetable for its dissemination. The Pharmacovigilance Risk Assessment Committee shall, at the request of the Agency, provide advice on those safety announcements.

6. Where the competent authorities of the Member States or the Agency, as applicable, make information referred to in paragraphs 2 and 3 publicly available, any personal data or data of a commercially confidential nature shall be deleted unless its public disclosure is necessary for the protection of public health.

SECTION 3

RECORDING AND REPORTING OF SUSPECTED ADVERSE REACTIONS

Article 108

Recording and reporting of suspected adverse reactions by the marketing authorisation holder

1. Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries that are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study including data relating to suspected adverse reactions occurring where the product is used outside the terms of the marketing authorisation.

   Marketing authorisation holders shall ensure that those reports are accessible at a single point within the Union.

   By way of derogation from the first subparagraph, suspected adverse reactions occurring in the context of a clinical trial shall be recorded and reported in accordance with Regulation (EU) No 536/2014.

2. Marketing authorisation holders shall not refuse to consider reports of suspected adverse reactions received electronically or by any other appropriate means from patients, who may be assisted by other persons, or healthcare professionals, including reports received in accordance with Article 109.

3. Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 103 of Regulation (EU) 2026/…[+] ('Eudravigilance database') information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

Marketing authorisation holders shall submit electronically to the Eudravigilance database information on all non-serious suspected adverse reactions that occur in the Union, within 90 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

For medicinal products containing active substances referred to in the list of medical literature monitored by the Agency pursuant to Article 108 of Regulation (EU) 2026/…[+], marketing authorisation holders shall not be required to submit to the Eudravigilance database the suspected adverse reactions recorded in that listed medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions recorded therein.

4. Marketing authorisation holders shall establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports. They shall also collect follow-up information and submit the updates electronically to the Eudravigilance database. Reports obtained from the Eudravigilance database shall not be re-submitted by the marketing authorisation holders to the Eudravigilance database, unless they contain additional information.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

5. Marketing authorisation holders shall collaborate with the competent authorities of the Member States and the Agency in the detection of duplicates of suspected adverse reaction reports.

6. This Article shall apply *mutatis mutandis* to undertakings supplying medicinal products used in accordance with Article 4, paragraph 1 or 4.

Article 109

Recording and reporting of suspected adverse reactions by wholesale distributors

Wholesale distributors that distribute medicinal products in accordance with Article 165(3) to (6) shall record all suspected adverse reactions with regard to those medicinal products which are brought to their attention, whether reported spontaneously by patients or by healthcare professionals, including suspected adverse reactions occurring where the product is used outside the terms of the marketing authorisation. They shall transmit those reports immediately to the marketing authorisation holder holding the marketing authorisation in the source Member State referred to in Article 165(3).

Article 110

Recording and reporting of suspected adverse reactions by Member States

1. Each Member State shall record all suspected adverse reactions that occur in its territory which are brought to its attention by healthcare professionals and patients. This shall include all authorised medicinal products and medicinal products used in accordance with Article 4, paragraph 1 or 4. Member States shall involve patients and healthcare professionals, as appropriate, in the follow-up of any reports they receive in order to comply with Article 100(1), points (c) and (e).

   Member States shall ensure that reports of such reactions may be submitted by means of the national medicines web portals or by other means.

2. For reports submitted by a marketing authorisation holder, Member States on whose territory the suspected adverse reaction occurred may involve the marketing authorisation holder in the follow-up of the reports.

3. Member States shall collaborate with the Agency and the marketing authorisation holders in the detection of duplicates of suspected adverse reaction reports.

4. Member States shall, within 15 days of the receipt of the reports of serious suspected adverse reactions referred to in paragraph 1, submit the reports electronically to the Eudravigilance database.

Member States shall, within 90 days of the receipt of the reports referred to in paragraph 1, submit reports of non-serious suspected adverse reactions electronically to the Eudravigilance database.

Marketing authorisation holders and marketing authorisation applicants to the extent necessary shall have access to the reports referred to in this paragraph through the Eudravigilance database.

5. Member States shall ensure that reports of suspected adverse reactions arising from an error associated with the use of a medicinal product that are brought to their attention are submitted electronically to the Eudravigilance database and made available to any authorities, bodies, organisations or institutions responsible for patient safety within the Member State concerned. They shall also ensure that the authorities responsible for medicinal products within that Member State are informed of any suspected adverse reactions brought to the attention of any other authority within that Member State. These reports shall be appropriately identified in the forms referred to in Article 104 of Regulation (EU) 2026/…[+].

6. Unless there are justifiable grounds resulting from pharmacovigilance activities, Member States shall not impose any additional obligations on marketing authorisation holders for the reporting of suspected adverse reactions.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

SECTION 4

PERIODIC SAFETY UPDATE REPORTS

Article 111

Periodic safety update reports

1. Marketing authorisation holders shall submit electronically to the Agency periodic safety update reports containing:

   (a) summaries of data relevant to the benefit-risk balance of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation;

   (b) a scientific evaluation of the benefit-risk balance of the medicinal product;

   (c) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorisation holder relating to the volume of medical prescriptions, including an estimate of the population exposed to the medicinal product.

   The data provided in accordance with the first subparagraph, point (c), shall differentiate between sales and volumes generated within the Union and those generated outside the Union.

2. The evaluation referred to in paragraph 1, first subparagraph, point (b), shall be based on all available data, including data from clinical trials in unauthorised therapeutic indications and populations.

3. The Agency shall make available the periodic safety update reports referred to in paragraph 1 to the competent authorities of the Member States, the members of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group by means of the repository for periodic safety update reports set up under Article 105 of Regulation (EU) 2026/…[+].

4. By way of derogation from paragraph 1, the marketing authorisation holders for medicinal products referred to in Article 10 or 14 shall only be required to submit periodic safety update reports for such medicinal products to the competent authority of the Member State or the Agency, as applicable, in the following cases:

   (a) where such obligation has been laid down as a condition in the marketing authorisation in accordance with Article 47 or 48; or

   (b) when requested by the competent authority of a Member State or the Agency, as applicable, on the basis of concerns relating to pharmacovigilance data or due to the lack of periodic safety update reports relating to an active substance after the marketing authorisation has been granted.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

By way of derogation from paragraph 1, the registration holders for medicinal products referred to in Article 130 or Article 138(1), shall only be required to submit periodic safety update reports for such medicinal products when requested by the competent authority of a Member State on the basis of concerns relating to pharmacovigilance data.

The assessment reports of the periodic safety update reports referred to in the first subparagraph of this paragraph shall be communicated by the competent authority of a Member State or the Agency, as applicable, to the Pharmacovigilance Risk Assessment Committee, which shall consider whether there is a need for a single assessment report for all marketing authorisations for medicinal products containing the same active substance and which shall inform the coordination group or the Committee for Medicinal Products for Human Use accordingly, in order to apply the procedures laid down in Article 112(4) and Article 114.

Article 112

Frequency of periodic safety update reports

1. The frequency with which the periodic safety update reports referred to in Article 111 are to be submitted shall be specified in the marketing authorisation.

The dates of submission of the periodic safety update reports according to the specified frequency shall be calculated from the date when then marketing authorisation was granted.

2. Holders of marketing authorisations which have been granted before 21 July 2012, and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation, shall submit the periodic safety update reports in accordance with the second subparagraph of this paragraph unless another frequency or other dates of submission of the reports are set in the marketing authorisation or determined in accordance with paragraphs 4, 5 and 6.

Periodic safety update reports shall be submitted to the competent authorities of the Member States or the Agency, as applicable, immediately upon request or in accordance with the following:

(a) where a medicinal product has not yet been placed on the market, at least every six months following the granting of the marketing authorisation and until the placing on the market;

(b) where a medicinal product has been placed on the market, once a year during the first five years following the initial placing on the market, and at three-yearly intervals for the subsequent six years and with a five-year interval thereafter.

3. Paragraph 2 shall also apply to medicinal products that are authorised only in one Member State and for which paragraph 4 does not apply.

4. Where medicinal products that are subject to different marketing authorisations contain the same active substance or the same combination of active substances, the frequency and dates of submission of the periodic safety update reports resulting from the application of paragraphs 1 and 2 may be amended and harmonised to enable a single assessment to be made in the context of a periodic safety update report work-sharing procedure and to set a Union reference date from which the dates of submission of the reports are calculated.

The harmonised frequency for the submission of the reports and the Union reference date may be determined, after consultation of the Pharmacovigilance Risk Assessment Committee, by one of the following:

(a) the Committee for Medicinal Products for Human Use, where at least one of the marketing authorisations for the medicinal products containing the active substance concerned has been granted in accordance with the centralised procedure provided for in Article 3 of Regulation (EU) 2026/…[+];

(b) the coordination group, in other cases than those referred to in point (a).

The harmonised frequency for the submission of the reports determined pursuant to this paragraph shall be made publicly available by the Agency. Marketing authorisation holders shall submit an application for a variation of the marketing authorisation accordingly.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

5. For the purposes of paragraph 4, the Union reference date for medicinal products containing the same active substance or the same combination of active substances shall be one of the following:

(a) the date when the first marketing authorisation was granted in the Union for a medicinal product containing that active substance or that combination of active substances;

(b) if the date referred to in point (a) cannot be ascertained, the earliest of the known dates of the marketing authorisations for a medicinal product containing that active substance or that combination of active substances.

6. Marketing authorisation holders shall be allowed to submit requests to the Committee for Medicinal Products for Human Use or the coordination group, as appropriate, to determine Union reference dates or to change the frequency of submission of periodic safety update reports on one of the following grounds:

(a) for reasons relating to public health;

(b) in order to avoid a duplication of the assessment;

(c) in order to achieve international harmonisation.

Such requests shall be submitted in writing and shall be duly justified. The Committee for Medicinal Products for Human Use or the coordination group shall, following the consultation with the Pharmacovigilance Risk Assessment Committee, either approve or deny such requests. Any change to the Union reference dates or the frequency of submission of periodic safety update reports shall be made publicly available by the Agency. The marketing authorisation holders shall submit an application for a variation of the marketing authorisation accordingly.

7. The Agency shall make public a list of Union reference dates and frequency of submission of periodic safety update reports by means of the European medicines web portal.

Any change to the frequency or dates of submission of periodic safety update reports specified in the marketing authorisation as a result of the application of paragraphs 4, 5 and 6 shall take effect four months from the date of the publication referred to in the first subparagraph.

Article 113

Assessment of periodic safety update reports

The competent authorities of the Member State shall assess periodic safety update reports to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products.

Article 114

Single assessment of periodic safety update reports

1. A single assessment of periodic safety update reports shall be performed for medicinal products authorised in more than one Member State and, in the cases referred to in Article 112, paragraphs 4, 5 and 6, for all medicinal products containing the same active substance or the same combination of active substances and for which a Union reference date and a frequency for the submission of periodic safety update reports have been established.

The single assessment shall be conducted by either of the following:

(a) a Member State appointed by the coordination group where none of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Article 3 of Regulation (EU) 2026/…[+];

(b) a rapporteur appointed by the Pharmacovigilance Risk Assessment Committee, where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Article 3 of Regulation (EU) 2026/…[+].

When selecting the Member State in accordance with the second subparagraph, point (a), the coordination group shall take into account whether any Member State is acting as a reference Member State, in accordance with Chapter III, Sections 3 and 4.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

2. The Member State or rapporteur, as applicable, shall draw up an assessment report within 60 days of receipt of the periodic safety update report and send it to the Agency and to the Member States concerned. The Agency shall send the report to the marketing authorisation holder.

Within 30 days of receipt of the assessment report, the Member States and the marketing authorisation holder may submit comments to the Agency and to the Member State or rapporteur. Where the report includes questions addressed to the marketing authorisation holder, the marketing authorisation holder shall provide answers within those 30 days.

3. Within 15 days of receipt of the comments referred to in paragraph 2, second subparagraph, the Member State or rapporteur shall update the assessment report, taking into account any comments submitted, and forward it to the Pharmacovigilance Risk Assessment Committee. The Pharmacovigilance Risk Assessment Committee shall adopt the assessment report with or without further changes at its next meeting and issue a recommendation. The recommendation shall mention any divergent positions and the grounds on which they are based.

The Agency shall include the adopted assessment report and the recommendation in the repository for periodic safety update reports set up under Article 105 of Regulation (EU) 2026/…[+] and forward them to the marketing authorisation holder.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

Article 115

Regulatory action on periodic safety update reports

Following the assessment of periodic safety update reports referred to in Article 113, the competent authorities of the Member States shall consider whether any action concerning the marketing authorisation for the medicinal product concerned is necessary and shall maintain, vary, suspend or revoke the marketing authorisation as appropriate.

Article 116

Procedure for regulatory action on periodic safety update reports

1. In the case of a single assessment of periodic safety update reports in accordance with Article 114(1) which recommends action concerning more than one marketing authorisation that does not include any centralised marketing authorisation, the coordination group shall, within 30 days of receipt of the assessment report of the Pharmacovigilance Risk Assessment Committee, consider the assessment report and reach a position on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the agreed position.

2. If, within the coordination group, the Member States represented reach an agreement by consensus on the action to be taken, the chairperson shall acknowledge the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary, suspend or revoke the marketing authorisations concerned in accordance with the timetable for implementation determined in the agreement.

In the event a variation is agreed upon, the marketing authorisation holder shall submit to the competent authorities of the Member States an appropriate application for a variation, including an updated summary of product characteristics and an updated package leaflet within the determined timetable for implementation.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in Article 45.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee referred to in Article 114(3), the coordination group shall attach to the agreement or the majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

3. In the case of a single assessment of periodic safety update reports in accordance with Article 114(1) that recommends action concerning more than one marketing authorisation that includes at least one centralised marketing authorisation, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the assessment report of the Pharmacovigilance Risk Assessment Committee, consider the assessment report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the opinion.

4. Where the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3 differs from the recommendation of the Pharmacovigilance Risk Assessment Committee referred to in Article 114(3), the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

5. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall, by means of implementing acts:

   (a) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations granted by the Member States and concerned by the procedure provided for in this section; and

   (b) where the opinion states that regulatory action concerning the marketing authorisation is necessary, adopt a decision to vary, suspend or revoke the centralised marketing authorisations concerned by the procedure provided for in this section.

6. Article 45 shall apply to the adoption of the decision referred to in paragraph 5, point (a), of this Article and to its implementation by the Member States.

7. Article 14 of Regulation (EU) 2026/…[+] shall apply to the decision referred to in paragraph 5, point (b), of this Article. Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 59 of Regulation (EU) 2026/…[+].

SECTION 5

SIGNAL DETECTION

Article 117

Signal monitoring and detection

1. Regarding medicinal products authorised in accordance with Chapter III, the competent authorities of the Member States shall, in collaboration with the Agency, take the following measures:

   (a) monitor the outcome of risk minimisation measures contained in risk management plans and of the conditions referred to in Article 47(1), points (a) to (g) and (i), and in Article 48 and any obligations imposed in accordance with Article 89(1) points (a), (b) and (c);

   (b) assess updates of the risk management system;

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(c) monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks have an impact on the benefit-risk balance.

2. The Pharmacovigilance Risk Assessment Committee shall perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the benefit-risk balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement on any subsequent action concerning the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue. Where appropriate, the assessment of those signals may be included in a pending assessment of a periodic safety update report or a pending procedure in accordance with Articles 94 to 98 and 118, 119 and 120 of this Directive or Article 57 of Regulation (EU) 2026/…[+].

3. The Agency and competent authorities of the Member States and the marketing authorisation holder shall inform each other in the event of new risks or risks that have changed or changes to the benefit-risk balance being detected.

4. Member States shall ensure that marketing authorisation holders inform the Agency and competent authorities of the Member State in the event of new risks or risks that have changed or changes to the benefit-risk balance being detected.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

SECTION 6

URGENT UNION PROCEDURE

Article 118

Initiation of an urgent Union procedure

1. A Member State or the Commission, as appropriate, shall, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, initiate the procedure provided for in this Section (the 'urgent Union procedure') by informing the other Member States, the Agency and the Commission where:

   (a) it considers suspending or revoking a marketing authorisation;

   (b) it considers prohibiting the supply of a medicinal product;

   (c) it considers refusing the renewal of a marketing authorisation; or

   (d) it is informed by the marketing authorisation holder that, on the basis of safety concerns, the marketing authorisation holder has interrupted the placing on the market of a medicinal product or has taken action to have a marketing authorisation withdrawn, or intends to take such action or has not applied for the renewal of a marketing authorisation.

2. A Member State or the Commission, as appropriate, shall, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, inform the other Member States, the Agency and the Commission where it considers that a new contraindication, a reduction in the recommended dose or a restriction to the therapeutic indications of a medicinal product is necessary. The information shall outline the action considered and the reasons therefor.

Any Member State or the Commission, as appropriate, shall, when urgent action is considered necessary in any of the cases referred to in the first subparagraph, initiate the urgent Union procedure.

Where the urgent Union procedure is not initiated, for medicinal products authorised in accordance with Chapter III, Sections 3 and 4, the matter shall be brought to the attention of the coordination group.

Article 98 shall apply where the interests of the Union are involved.

3. Where the urgent Union procedure is initiated, the Agency shall verify whether the safety concern relates to medicinal products other than the one covered by the information referred to in paragraphs 1 and 2, or whether the safety concern is common to all medicinal products belonging to the same range or therapeutic class.

Where the medicinal product involved is authorised in more than one Member State, the Agency shall without undue delay inform the initiator of the urgent Union procedure referred to in paragraph 2, second subparagraph, of the outcome of the verification, and the procedures laid down in Articles 119 and 120 shall apply. Otherwise, the safety concern shall be addressed by the Member State concerned. The Agency or the Member State, as applicable, shall make the information that the urgent Union procedure has been initiated available to marketing authorisation holders.

4. Without prejudice to paragraphs 1 and 2 of this Article and Articles 119 and 120, a Member State may, where urgent action is necessary to protect public health, suspend the marketing authorisation and prohibit the use of the medicinal product concerned on its territory until a definitive decision is adopted in the urgent Union procedure. It shall inform the Commission, the Agency and the other Member States no later than the following working day of the reasons for its action.

5. At any stage of the procedure laid down in Articles 119 and 120, the Commission may request a Member State in which the medicinal product is authorised to take temporary measures immediately.

Where the scope of the procedure, as determined in accordance with paragraphs 1 and 2, includes medicinal products covered by centralised marketing authorisations, the Commission may, at any stage of the urgent Union procedure, take temporary measures immediately in relation to those marketing authorisations.

6. The information referred to in paragraphs 1 and 2 may relate to individual medicinal products or to a range of medicinal products or a therapeutic class.

If the Agency identifies that the safety concern relates to more medicinal products than those that are covered by the information referred to in paragraphs 1 and 2 or that the safety concern is common to all medicinal products belonging to the same range or therapeutic class, it shall extend the scope of the procedure accordingly.

Where the scope of the urgent Union procedure concerns a range of medicinal products or a therapeutic class, medicinal products covered by the centralised marketing authorisation that belong to that range of medicinal products or therapeutic class shall also be included in the procedure.

7. At the time the information referred to in paragraphs 1 and 2 is provided, the Member State shall make available to the Agency all relevant scientific information that it has at its disposal and any assessment by the Member State.

Article 119

Urgent Union procedure scientific assessment

1. Following receipt of the information referred to in Article 118, paragraphs 1 and 2, the Agency shall publicly announce the initiation of the urgent Union procedure by means of the European medicines web portal. In parallel, Member States may publicly announce the initiation of the urgent Union procedure on their national medicines web portals.

The announcement shall specify the matter submitted to the Agency in accordance with Article 118, and the medicinal products and, where applicable, the active substances concerned. It shall contain information on the right of the marketing authorisation holders, healthcare professionals and the public to submit to the Agency information relevant to the procedure and it shall state how such information may be submitted.

2. The Pharmacovigilance Risk Assessment Committee shall assess the matter that has been submitted to the Agency in accordance with Article 118. The rapporteur appointed by the Pharmacovigilance Risk Assessment Committee in accordance with Article 159 of Regulation (EU) 2026/…[+], shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use in accordance with Article 159 of Regulation (EU) 2026/…[+] and with the reference Member State for the medicinal products concerned.

For the purposes of the assessment referred to in the first subparagraph, the marketing authorisation holder may submit comments in writing.

Where the urgency of the matter permits, the Pharmacovigilance Risk Assessment Committee may hold public hearings, where it considers that this is appropriate on justified grounds particularly with regard to the extent and seriousness of the safety concern. The hearings shall be held in accordance with the modalities specified by the Agency and shall be announced by means of the European medicines web portal. In the hearing, the Pharmacovigilance Risk Assessment Committee shall also give due regard to the therapeutic effect and clinical context of the medicinal product. The announcement shall specify the modalities of participation.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

The Agency shall, in consultation with the parties concerned, draw up rules of procedure on the organisation and conduct of public hearings, in accordance with Article 153(1) of Regulation (EU) 2026/…[+].

Where a marketing authorisation holder or another person intending to submit information, has confidential data relevant to the subject matter of the procedure, they may request permission to present those data to the Pharmacovigilance Risk Assessment Committee in a non-public hearing.

3. Within 60 days of the submission of the information, the Pharmacovigilance Risk Assessment Committee shall make a recommendation, stating the reasons on which it is based, having due regard to the therapeutic effect of the medicinal product. The recommendation shall mention any divergent positions and the grounds on which they are based. In the case of urgency, and on the basis of a proposal by its chairperson, the Pharmacovigilance Risk Assessment Committee may agree to a shorter deadline. The recommendation shall include any or a combination of the following conclusions:

(a) no further evaluation or action is required at Union level;

(b) the marketing authorisation holder should conduct further evaluation of data and carry out a follow-up of the results of that evaluation;

(c) the marketing authorisation holder should sponsor a post-authorisation safety study and carry out a follow up evaluation of the results of that study;

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(d) the Member States or marketing authorisation holder should implement risk minimisation measures;

(e) the marketing authorisation should be suspended, revoked or not renewed;

(f) the marketing authorisation should be varied.

4. For the purposes of paragraph 3, point (d), the recommendation shall specify the risk minimisation measures recommended and any conditions or restrictions to which the marketing authorisation should be made subject, including the timeline for implementation.

5. For the purposes of paragraph 3, point (f), where it is recommended to change or add information in the summary of product characteristics or the labelling or package leaflet, the recommendation shall suggest the wording of such changed or added information and shall indicate where in the summary of product characteristics, the labelling or package leaflet such wording should be placed.

Article 120

Follow-up of recommendation made in the framework of the urgent Union procedure

1. Where the scope of the urgent Union procedure, as determined in accordance with Article 118(6), does not include any centralised marketing authorisation, the coordination group shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee referred to in Article 119(3), consider the recommendation and reach a position on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisation concerned, including a timetable for the implementation of the agreed position. Where an urgent adoption of the position is necessary, the coordination group may, on the basis of a proposal by its chairperson, agree to a shorter deadline.

2. If, within the coordination group, the Member States represented reach an agreement on the action to be taken by consensus, the chairperson shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary, suspend, revoke or refuse renewal of the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

   In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the competent authorities of the Member States an appropriate application for a variation, including an updated summary of product characteristics and an updated package leaflet within the determined timetable for implementation.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in Article 45.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of the Member States represented within the coordination group differs from the recommendation of the Pharmacovigilance Risk Assessment Committee referred to in Article 119(3), the coordination group shall attach to the agreement or the majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

3. Where the scope of the procedure, as determined in accordance with Article 118(6), includes at least one centralised marketing authorisation, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee referred to in Article 119(3), consider the recommendation and adopt an opinion on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisations concerned. Where an urgent adoption of the opinion is necessary, the Committee for Medicinal Products for Human Use may, on the basis of a proposal by its chairperson, agree to a shorter deadline.

Where the opinion of the Committee for Medicinal Products for Human Use referred to in the first subparagraph of this paragraph differs from the recommendation of the Pharmacovigilance Risk Assessment Committee referred to in Article 119(3), the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall, by means of implementing acts:

(a) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations that are granted by the Member States and that are subject to the urgent Union procedure;

(b) where the opinion states that regulatory action concerning the marketing authorisation is necessary, adopt a decision to vary, suspend, revoke or refuse the renewal of the centralised marketing authorisations concerned by the Union urgent procedure.

5. Article 45 shall apply to the adoption of the decision referred to in paragraph 4, point (a), of this Article and to its implementation by the Member States.

6. Article 14 of Regulation (EU) 2026/…[+] shall apply to the decision referred to in paragraph 4, point (b), of this Article. Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 59 of Regulation (EU) 2026/…[+].

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

SECTION 7

SUPERVISION OF NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDIES

Article 121

Non-interventional post-authorisation safety studies

1. This Section applies to non-interventional post-authorisation safety studies that are initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed in accordance with Article 47 or 89, and that involve the collection of safety data from patients or healthcare professionals.

2. This Section is without prejudice to Member States and Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.

3. The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.

4. Payments to healthcare professionals for participating in non-interventional post-authorisation safety studies shall be restricted to the compensation for time and expenses incurred.

5. The competent authority of the Member State may require the marketing authorisation holder to submit the protocol and the progress reports to the competent authorities of the Member States in which the study is conducted.

6. The marketing authorisation holder shall send the final report of the study to the competent authorities of the Member States in which the study was conducted within 12 months of the end of data collection.

7. While a study is being conducted, the marketing authorisation holder shall monitor the data generated and consider its implications for the benefit-risk balance of the medicinal product concerned.

Any new information that might influence the evaluation of the benefit-risk balance of the medicinal product shall be communicated to the competent authorities of the Member States in which the medicinal product has been authorised in accordance with Article 92.

The obligation laid down in the second subparagraph of this paragraph is without prejudice to the information on the results of studies that the marketing authorisation holder shall make available by means of the periodic safety update reports as laid down in Article 111.

8. Articles 122 to 125 shall apply exclusively to studies referred to in paragraph 1 of this Article that are conducted pursuant to an obligation imposed in accordance with Article 47 or 89.

Article 122

Agreement of a protocol for a non-interventional post-authorisation safety study

1. Before a study is conducted, the marketing authorisation holder shall submit a draft protocol to the Pharmacovigilance Risk Assessment Committee, except for studies to be conducted in only one Member State that requires the study in accordance with Article 89. For such studies, the marketing authorisation holder shall submit a draft protocol to the competent authority of the Member State in which the study is conducted.

2. Within 60 days of the submission of the draft protocol referred to in paragraph 1, the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall issue:

   (a) a letter endorsing the draft protocol;

   (b) a letter of objection, which shall set out in detail the grounds for the objection, where:

      (i) it considers that the conduct of the study promotes the use of a medicinal product;

      (ii) it considers that the design of the study does not fulfil the study objectives; or

   (c) a letter notifying the marketing authorisation holder that the study is a clinical trial falling under the scope of Regulation (EU) No 536/2014.

3. The study may commence only when the written endorsement from the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee, as appropriate, has been issued.

Where a letter of endorsement of the draft protocol as referred to in paragraph 2, point (a), has been issued, the marketing authorisation holder shall forward the protocol to the competent authorities of the Member States in which the study is to be conducted and may thereafter commence the study according to the endorsed protocol.

Article 123

Update of a protocol for a non-interventional post-authorisation safety study

After a study has been commenced, any substantial amendments to the protocol shall be submitted, before their implementation, to the competent authority of the Member State or to the Pharmacovigilance Risk Assessment Committee, as appropriate. The competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall assess the amendments and inform the marketing authorisation holder of its endorsement or objection. Where applicable, the marketing authorisation holder shall inform the Member States in which the study is conducted.

Article 124

Final study report on a non-interventional post-authorisation safety study

1. Upon completion of the study, the marketing authorisation holder shall submit a final study report to the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee, as appropriate, within 12 months of the end of data collection unless a written waiver has been granted by the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee, as appropriate.

2. The marketing authorisation holder shall evaluate whether the results of the study have an impact on the marketing authorisation and shall, if necessary, submit to the competent authorities of the Member States an application to vary the marketing authorisation.

3. Together with the final study report, the marketing authorisation holder shall electronically submit an abstract of the study results to the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee, as appropriate.

Article 125

Recommendations following the submission of a final study report on non-interventional post-authorisation safety studies

1. Based on the results of the study and after consultation of the marketing authorisation holder, the Pharmacovigilance Risk Assessment Committee may make recommendations concerning the marketing authorisation, stating the reasons on which they are based. The recommendations shall mention any divergent positions and the grounds on which they are based.

2. When recommendations for the variation, suspension or revocation of a national marketing authorisation are made pursuant to paragraph 1, the Member States represented within the coordination group shall agree on a position on the matter taking into account the recommendations referred to in paragraph 1 and shall include a timetable for the implementation of the agreed position.

If, within the coordination group, the Member States represented reach an agreement on the action to be taken by consensus, the chairperson shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to vary, suspend or revoke the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the competent authorities of the Member State an appropriate application for a variation, including an updated summary of product characteristics and an updated package leaflet within the determined timetable for implementation.

The agreement shall be made publicly available on the European medicines web portal established in accordance with Article 106 of Regulation (EU) 2026/…[+].

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

3. If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group, together with a detailed description of the matters on which the Member States have been unable to reach an agreement, all the divergent positions of Member States presented and the scientific grounds on which they are based, shall be forwarded to the Commission, which shall apply the procedure laid down in Article 45.

4. Where the agreement reached by the Member States represented within the coordination group or the position of the majority of the Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee referred to in paragraph 1, the coordination group shall attach to the agreement or the majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

SECTION 8

IMPLEMENTATION, GUIDANCE AND REPORTING

Article 126

Implementing acts related to pharmacovigilance activities

1. In order to harmonise the performance of the pharmacovigilance activities provided for in this Directive, the Commission shall adopt implementing acts in the following areas for which pharmacovigilance activities are provided for in Articles 99, 102, 103, 108 to 111, 117, 122 and 124 and in points (14), (15) and (16) of Annex I, setting out:

   (a) the content and the rules on the maintenance of the pharmacovigilance system master file kept by the marketing authorisation holder;

   (b) minimum requirements for the quality system for the performance of pharmacovigilance activities by the competent authorities of the Member States and the marketing authorisation holder;

   (c) rules on the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities;

   (d) minimum requirements for the monitoring of data in the Eudravigilance database to determine whether there are new risks or whether risks have changed;

   (e) the format and content of the electronic transmission of suspected adverse reactions by Member States and the marketing authorisation holder;

(f) the format and content of electronic periodic safety update reports and risk management plans;

(g) the format of protocols, abstracts and final study reports for the non-interventional post-authorisation safety studies.

2. The implementing acts referred to in paragraph 1 shall take account of the work on international harmonisation carried out in the area of pharmacovigilance and shall, where necessary, be revised to take account of technical and scientific progress. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 217(2).

Article 127

Guidance to facilitate the performance of pharmacovigilance activities

The Agency shall, in cooperation with the competent authorities of the Member States and other interested parties, draw up:

(a) guidance on good pharmacovigilance practice for the competent authorities of the Member States, the Agency and marketing authorisation holders;

(b) scientific guidance on post-authorisation efficacy studies.

Article 128

Reporting on pharmacovigilance tasks

The Agency shall make public a report on the performance of pharmacovigilance tasks by the Member States and the Agency every three years. The first report shall be made public by … [five years from the date of entry into force of this Directive].

Chapter X
Homeopathic medicinal products and traditional herbal medicinal products

SECTION 1
SPECIFIC PROVISIONS APPLICABLE TO HOMEOPATHIC MEDICINAL PRODUCTS

Article 129

Registration or authorisation of homeopathic medicinal products

1. Member States shall ensure that homeopathic medicinal products manufactured and placed on the market in the Union are registered in accordance with Articles 130 and 131 or authorised in accordance with Article 137(1), except where such homeopathic medicinal products are covered by a registration or authorisation granted in accordance with national legislation on or before 31 December 1993. In the case of registrations, Chapter III, Sections 3 and 4, and Article 41(1), (2) and (3) shall apply *mutatis mutandis*.

2. Member States shall establish a simplified registration procedure as referred to in Article 130 for homeopathic medicinal products.

Article 130

Simplified registration procedure for homeopathic medicinal products

1. Homeopathic medicinal products that satisfy all of the following conditions may be subject to a simplified registration procedure:

   (a) they are administered orally or externally;

   (b) no specific therapeutic indication appears in the labelling of the homeopathic medicinal product, is conveyed in the name of the homeopathic medicinal products, or in any information relating thereto;

   (c) there is a sufficient degree of dilution to guarantee the safety of the homeopathic medicinal product.

2. For the purposes of paragraph 1, point (c), the homeopathic medicinal product shall not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a medical prescription.

3. The Commission is empowered to adopt delegated acts in accordance with Article 218 to amend paragraph 2 of this Article, in order to take account of scientific progress.

At the time of registration, Member States shall determine the prescription status for the dispensing of the homeopathic medicinal product.

4. The criteria and rules of procedure provided for in Article 1(9), Article 33, Chapter III, Section 6 and Articles 194, 198 and 205 shall apply *mutatis mutandis* to the simplified registration procedure for homeopathic medicinal products, with the exception of the proof of therapeutic efficacy.

Article 131

Application requirements for simplified registration

1. The holder of a homeopathic medicinal product simplified registration shall be established in the Union.

2. An application for a simplified registration may cover a series of homeopathic medicinal products derived from the same homeopathic stock or stocks. The following shall be included with the application in order to demonstrate, in particular, the pharmaceutical quality and the batch-to-batch homogeneity of the homeopathic medicinal products concerned:

   (a) the scientific name or other name given in a pharmacopoeia of the homeopathic stock or stocks, together with a statement of the various routes of administration, pharmaceutical forms and degree of dilution to be registered;

(b) a dossier describing how the homeopathic stock or stocks are obtained and controlled, and justifying their homeopathic use, on the basis of an adequate bibliography;

(c) the manufacturing and control file for each pharmaceutical form and a description of the method of dilution and potentisation;

(d) if the homeopathic medicinal product contains biological substances, documentation on the measures taken to ensure its absence of pathogens;

(e) the manufacturing authorisation for the homeopathic medicinal product concerned;

(f) the copies or references to identify any registrations or authorisations obtained for the same homeopathic medicinal product in other Member States;

(g) one or more mock-ups of the outer packaging and the immediate packaging of the homeopathic medicinal products to be registered;

(h) the data concerning the stability of the homeopathic medicinal product and shelf life of the homeopathic medicinal product;

(i) name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.

Article 132

Application of decentralised and mutual recognition procedures to homeopathic medicinal products

1. Article 41(4) and (5), Articles 42 to 45 and 98 shall not apply to the homeopathic medicinal products referred to in Article 130(1).

2. Chapter III, Sections 3 to 5, shall not apply to the homeopathic medicinal products referred to in Article 137(1).

Article 133

Labelling of homeopathic medicinal products

Homeopathic medicinal products, with the exception of those referred to in Article 130(1), shall be labelled in accordance with Chapter VI and shall be identified by a reference on their labels, in clear and legible form, to their homeopathic nature.

Article 134

Specific requirements for labelling of certain homeopathic medicinal products

1. The labelling and, where appropriate, the package insert for homeopathic medicinal products referred to in Article 130(1) in addition to the clear mention of the words 'homeopathic medicinal product', shall bear the following, and no other, information:

   (a) the scientific name of the stock or stocks followed by the degree of dilution, making use of the symbols of the pharmacopoeia used in accordance with Article 5(1) point (67);

(b) name and address of the registration holder and, where appropriate, of the manufacturer;

(c) method of administration and, if necessary, route of administration;

(d) pharmaceutical form and the content by weight, volume or number of doses of the homeopathic medicinal product;

(e) expiry date, in clear terms (month, year);

(f) special storage precautions, if any;

(g) a special warning if necessary for the homeopathic medicinal product;

(h) manufacturer's batch number;

(i) registration number;

(j) the statement 'homeopathic medicinal product without approved therapeutic indications';

(k) a warning advising the patients not to interrupt any ongoing medical treatment prescribed or instructed by healthcare professionals, when taking the homeopathic medicinal product.

(l) for the package insert: the date on which the package insert was last revised;

(m) the list of those excipients known to have a recognised action or effect and included in the detailed guidance published pursuant to Article 80.

As regards the first subparagraph, point (a), if the homeopathic medicinal product is composed of two or more stocks, the scientific names of the stocks in the labelling may be supplemented by an invented name.

2. Notwithstanding paragraph 1, Member States may require the use of certain types of labelling in order to show:

(a) the price of the homeopathic medicinal product;

(b) the reimbursement conditions.

Article 135

Advertising of homeopathic medicinal products

Chapter XIII shall apply to all homeopathic medicinal products, with the exception of Article 179(1) which shall not apply to the homeopathic medicinal products referred to in Article 130(1). However, only the information specified in Article 134(1) shall be used in the advertising of the homeopathic medicinal products referred to in Article 130(1).

Article 136

Exchange of information on homeopathic medicinal products

Member States shall communicate to each other all the information necessary to guarantee the quality and safety of homeopathic medicinal products manufactured and marketed within the Union, and in particular the information referred to in Articles 205 and 206.

Article 137

Other requirements for homeopathic medicinal products

1. Homeopathic medicinal products other than those referred to in Article 130(1) shall be granted a marketing authorisation in accordance with Articles 7 and 10 to 15.

2. A Member State may introduce or retain in its territory specific rules for the non-clinical tests and clinical studies of homeopathic medicinal products other than those referred to in Article 130(1), in accordance with the principles and characteristics of homeopathy as practised in that Member State.

   In this case, the Member State concerned shall notify the Commission of the specific rules in force.

3. Chapter IX shall apply to homeopathic medicinal products, with the exception of those referred to in Article 130(1). Chapter XI, Chapter XII, Section 1, and Chapter XIV shall apply to homeopathic medicinal products.

SECTION 2

SPECIFIC PROVISIONS

APPLICABLE TO TRADITIONAL HERBAL MEDICINAL PRODUCTS

Article 138

Simplified registration procedure for traditional herbal medicinal products

1. Herbal medicinal products that satisfy all of the following conditions may be subject to a simplified registration procedure ('traditional-use registration'):

   (a) they have therapeutic indications exclusively appropriate to traditional herbal medicinal products that, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment;

   (b) they are exclusively for administration in accordance with a specified strength and posology;

   (c) they are an oral, external or inhalation preparation;

   (d) the period of traditional use as laid down in Article 140(1), point (c), has elapsed;

   (e) the data on the traditional use of the herbal medicinal product referred to in Article 140(1), point (c), are sufficient.

The data on the traditional use of a herbal medicinal product referred to in the first subparagraph, point (e), shall be considered sufficient where the herbal medicinal product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the herbal medicinal product are plausible on the basis of long-standing use and experience.

2. The presence in the herbal medicinal product of vitamins or minerals for the safety of which there is well-documented evidence shall not prevent the herbal medicinal product from being eligible for registration in accordance with paragraph 1, provided that the action of the vitamins or minerals is ancillary to that of the herbal active substances regarding the specified claimed therapeutic indication(s).

3. However, in cases where the competent authorities of the Member States judge that a herbal medicinal product that fulfils the conditions laid down in paragraph 1 (‘traditional herbal medicinal product’) fulfils the criteria for a national marketing authorisation in accordance with Article 6 or for a simplified registration in accordance with Article 130, the provisions of this Section shall not apply.

Article 139

Submission of dossier for traditional herbal medicinal product

1. The applicant for and the holder of a traditional-use registration shall be established in the Union.

2. In order to obtain a traditional-use registration, the applicant shall submit an application for traditional-use registration to the competent authority of the Member State concerned.

Article 140

Application requirements for traditional-use registration

1. An application for traditional-use registration shall be accompanied by:

(a) the particulars and documents:

(i) referred to in points (1), (2), (3), (5) to (11), (16), (17) and (18) of Annex I;

(ii) the results of the pharmaceutical tests referred to in point (12)(a) of Annex I;

(iii) the summary of product characteristics, without the pharmacological properties as specified in Annex V, unless necessary for the safe use of the product;

(iv) in the case of combinations, as referred to in Article 5(1), point (69), or in Article 138(2), the information referred to in Article 138(1), first subparagraph, point (e), relating to the combination as such;

(b) any national marketing authorisation or registration obtained by the applicant in another Member State, or in a third country, to place the herbal medicinal product on the market, and details of any decision to refuse to grant a national marketing authorisation or registration, whether in the Union or a third country, and the reasons for any such decision;

(c) bibliographical or expert evidence to the effect that the herbal medicinal product in question, or a corresponding product, has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Union;

(d) a bibliographic review of safety data together with an expert report, and where required by the competent authority of the Member State, upon additional request, data necessary for assessing the safety of the herbal medicinal product.

For the purposes of the first subparagraph, point (a)(iv), if the individual active substances are not sufficiently known, the data shall also relate to the individual active substances.

For the purposes of the first subparagraph, point (c), at the request of the competent authority of a Member State where the application for traditional-use registration has been submitted, the Herbal Medicinal Products working group referred to in Article 145 (the 'Herbal Medicinal Products working group') shall draw up an opinion on the adequacy of the evidence of the long-standing use referred to in the first subparagraph, point (c), of the herbal medicinal product, or of the corresponding product. The competent authority of a Member State shall submit relevant documentation supporting the referral.

For the purposes of the first subparagraph, point (d), in the case of combinations, if the individual active substances are not sufficiently known, the safety data shall also relate to the individual active substances.

Annex II shall apply *mutatis mutandis* to the particulars and documents specified in the first subparagraph, point (a).

2. The requirement to show medicinal use throughout the period of at least 30 years, set out in paragraph 1, first subparagraph, point (c), is satisfied even where the marketing of the corresponding product has not been based on a specific authorisation. It is likewise satisfied where the number or quantity of ingredients of the corresponding product has been reduced during that period.

3. Where the corresponding product has been used in the Union for less than 15 years but is otherwise eligible for a traditional-use registration in accordance with paragraph 1, the competent authority of the Member State where the application for traditional-use registration has been submitted shall refer the application for traditional-use registration to the Herbal Medicinal Products working group and submit relevant documentation supporting this referral.

The Herbal Medicinal Products working group shall consider whether the criteria other than the period of traditional use for a traditional-use registration as referred to in Article 138 are complied with. If the Herbal Medicinal Products working group considers it possible, it shall establish a Union herbal monograph as referred to in Article 145(3) which shall be taken into account by the competent authority of Member State when taking its final decision on the application for traditional-use registration.

Article 141

Application of decentralised or mutual recognition marketing authorisation procedures to traditional herbal medicinal products

1. Chapter III, Sections 3 to 5, shall apply *mutatis mutandis* to traditional-use registrations granted in accordance with Article 138.

2. For traditional herbal medicinal products not covered by paragraph 1, the competent authority of each Member State shall, when evaluating an application for traditional-use registration, take due account of registrations granted by the competent authority of another Member State in accordance with this Section.

Article 142

Refusal of traditional-use registrations

1. Traditional-use registration shall be refused if the application does not comply with Article 138, 139 or 140 or if at least one of the following conditions is fulfilled:

   (a) the qualitative or quantitative composition is not as declared;

   (b) the therapeutic indications do not comply with the conditions laid down in Article 138;

   (c) the traditional herbal medicinal product could be harmful under normal conditions of use;

(d) the data on traditional use are insufficient, especially if pharmacological effects or efficacy are not plausible on the basis of long-standing use and experience;

(e) the pharmaceutical quality is not satisfactorily demonstrated or is inadequate.

2. The competent authorities of the Member States shall notify the applicant for traditional-use registration, the Commission and any competent authority of the Member State that requests it, of any decision they take to refuse traditional-use registration and the reasons for the refusal.

Article 143

List of herbal substances, herbal preparations and combinations thereof

1. The Commission shall adopt implementing acts to establish a list of herbal substances, herbal preparations and combinations thereof for use in traditional herbal medicinal products, taking into account the draft list prepared by the Herbal Medicinal Products working group. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 217(2). That list shall contain, with regard to each herbal substance, the therapeutic indications, the specified strength and the posology, the route of administration and any other information necessary for the safe use of the herbal substance as a traditional herbal medicinal product.

2. If an application for traditional-use registration relates to a herbal substance, a herbal preparation or a combination thereof contained in the list referred to in paragraph 1, the data specified in Article 140(1), points (b), (c) and (d), shall not be required and Article 142(1), points (c) and (d), shall not apply.

3. If a herbal substance, a herbal preparation or a combination is no longer included in the list referred to in paragraph 1, traditional-use registrations pursuant to paragraph 2 for herbal medicinal products containing this substance shall be revoked unless the particulars and documents referred to in Article 140(1) are submitted within three months.

Article 144

Other requirements for traditional herbal medicinal products

1. Article 1(5), points (a) and (b), Article 1(9), Articles 6 to 9, 32, 33, 47, 49, 60, 64, 91, 92, 94, 191, 194, 205, 206, 207 and 209 and Chapters IV, IX, XI, XII and XV of this Directive as well as Commission Directive (EU) 2017/1572[53] shall apply, *mutatis mutandis*, to traditional-use registrations granted under this Section.

2. In addition to the requirements set out in Articles 66 to 69, 73 to 82 and Annex IV, any labelling and package leaflet of a traditional herbal medicinal product shall contain a statement to the effect that:

   (a) the product is a traditional herbal medicinal product for use in specified therapeutic indication(s) exclusively based upon long-standing use; and

[53] Commission Directive (EU) 2017/1572 of 15 September 2017 supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for medicinal products for human use (OJ L 238, 16.9.2017, p. 44, ELI: http://data.europa.eu/eli/dir/2017/1572/oj).

(b) the user should consult a doctor or a qualified healthcare practitioner if the symptoms persist during the use of the traditional herbal medicinal product or if adverse effects not mentioned in the package leaflet occur.

A Member State may require that the labelling and the package leaflet also state the nature of the tradition in question.

3. In addition to the requirements set out in Chapter XIII, any advertisement for a traditional herbal medicinal product registered under this Section shall contain the following statement: 'Traditional herbal medicinal product for use in specified therapeutic indication(s) exclusively based upon long-standing use'.

Article 145

Herbal Medicinal Products working group

1. The Herbal Medicinal Products working group is hereby established. That working group shall be part of the Agency pursuant to Article 148, point (g), of Regulation (EU) 2026/…[+] and shall have the following competence:

(a) as regards traditional-use registrations, to:

(i) perform the tasks arising from Article 140(1) and (3);

(ii) prepare a draft list of herbal substances, herbal preparations and combinations thereof, as referred to in Article 143(1);

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(iii) establish Union monographs for traditional herbal medicinal products, as referred to in paragraph 3 of this Article;

(b) as regards marketing authorisations of herbal medicinal products, to establish Union herbal monographs for herbal medicinal products, as referred to in paragraph 3 of this Article;

(c) as regards referrals to the Agency under Chapter III, Section 5, or Article 98, in relation to traditional herbal medicinal products as referred to in Article 138, to perform the tasks set out in Article 44;

(d) where a matter concerning medicinal products containing herbal substances or herbal preparations, other than traditional herbal medicinal products, is referred to the Agency under Chapter III, Section 5, or Article 98, to give an opinion on the herbal substance, where appropriate.

Appropriate coordination with the Committee for Medicinal Products for Human Use shall be ensured by a procedure to be determined by the Executive Director of the Agency in accordance with Article 151(10), point (e), of Regulation (EU) 2026/…[+].

2. Each Member State shall appoint, for a three-year term which may be renewed, one member and one alternate to the Herbal Medicinal working group.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

The alternates shall represent and vote for the members in their absence. Members and alternates shall be chosen for their role and experience in the evaluation of herbal medicinal products and shall represent the competent authorities of the Member States.

The members of the Herbal Medicinal Products working group may be accompanied by experts in specific scientific or technical fields.

3. The Herbal Medicinal Products working group shall establish Union herbal monographs for herbal medicinal products with regard to applications submitted in accordance with Article 14 as well as for traditional herbal medicinal products.

Where the Union herbal monographs have been established, they shall be taken into account by the competent authorities of Member States when examining an application. Where no such Union herbal monograph has yet been established, other appropriate monographs, publications or data may be referred to.

When new Union herbal monographs are established, the traditional-use registration holder shall consider whether it is necessary to modify the registration dossier accordingly. The traditional-use registration holder shall notify any such modification to the competent authority of the Member State concerned.

The herbal monographs shall be published.

4. Article 153(3), (4) and (5) of Regulation (EU) 2026/…[+] shall apply *mutatis mutandis* to the Herbal Medicinal Products working group.

5. The Herbal Medicinal Products working group shall draft its rules of procedure.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

Chapter XI
Manufacturing and import

SECTION 1
MANUFACTURING AND IMPORT OF MEDICINAL PRODUCTS

Article 146

Manufacturing authorisation

1. Member States shall take all appropriate measures to ensure that the manufacture of medicinal products within their territory is subject to authorisation (the 'manufacturing authorisation'). A manufacturing authorisation shall be required also if the medicinal products manufactured are intended for export.

2. A manufacturing authorisation as referred to in paragraph 1 shall be required for both total and partial manufacture of medicinal products, including the various processes of dividing up, packaging or presentation.

   The manufacturing authorisation shall apply only to the categories of medicinal products, the pharmaceutical forms, the manufacturing operations and the premises specified in the application.

3. By way of derogation from paragraph 2, first subparagraph, no manufacturing authorisation shall be required for the following:

(a) the preparation, dividing up, changes to packaging or presentation where those processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes;

(b) manufacturing activities, including testing, carried out by decentralised sites, in accordance with Article 29 and Article 152, under the responsibility of the qualified person of a central site referred to in Article 155.

4. A manufacturing authorisation shall also be required for imports of medicinal products coming from third countries into a Member State.

This Chapter, Article 198(5) and Article 201 shall apply to imports of medicinal products from third countries.

5. Member States shall enter the information relating to the manufacturing authorisations in the Union database referred to in Article 191(15).

Article 147

Application for a manufacturing authorisation

1. In order to obtain a manufacturing authorisation, the applicant shall submit an application electronically to the competent authority of the Member State concerned. Member States may until … [seven years from the date of entry into force of this Directive] allow applications to be submitted in paper format.

The application for a manufacturing authorisation shall include the following particulars:

(a) the applicant's name or corporate name, as relevant, and permanent address;

(b) the medicinal products and pharmaceutical forms that are to be manufactured or imported and the manufacturing operations that are to be carried out and the place where the activities are to take place;

(c) proof that the applicant has at its disposal, for the purposes specified under point (b), suitable and sufficient premises, technical equipment and control facilities complying with the legal requirements that the Member State concerned lays down as regards manufacture of medicinal products, including storage, and control in accordance with this Directive;

(d) proof that the applicant has at its disposal the services of at least one qualified person within the meaning of Article 155.

2. In the case of an application for a manufacturing authorisation for a central site responsible for the supervision of decentralised manufacturing, the application shall also include:

(a) a description of all medicinal products that are subject to manufacturing steps in the decentralised sites, including the manufacturing activities, including testing, to be performed in relation to those medicinal products at the decentralised sites;

(b) proof that the applicant has at its disposal appropriate procedures and resources for the supervision of decentralised sites in accordance with Article 151(1), first subparagraph, point (e);

(c) for each decentralised site at the time of the application, a written confirmation by the qualified person referred to in Article 155 that the applicant has verified its compliance with the principles of good manufacturing practice referred to in Article 163 by conducting an audit.

3. The applicant shall provide electronically particulars in support of its application. Member States may until … [seven years from the date of entry into force of this Directive] allow particulars to be submitted in paper format.

Article 148

Granting of a manufacturing authorisation

1. The competent authority of the Member State shall carry out an inspection to confirm the accuracy of the particulars included in the application submitted in accordance with Article 147.

Where the accuracy of the particulars is confirmed in accordance with the first subparagraph, or in any event, no later than 90 days of the receipt of the application submitted in accordance with Article 147, the competent authority of the Member State shall grant or refuse a manufacturing authorisation.

By way of derogation from the second subparagraph, in justified cases, the inspection may be carried out after the manufacturing authorisation has been granted.

2. To ensure that the particulars referred to in Article 147 are duly provided, the competent authority of the Member State may grant a manufacturing authorisation subject to conditions.

Article 149

Changes to a manufacturing authorisation

If the manufacturing authorisation holder requests a change to any of the particulars referred to in Article 147(1), second subparagraph, and Article 147(2), points (a) and (b), the competent authority of the Member State shall take a decision on the requested change to the manufacturing authorisation no later than 30 days from such request. In exceptional cases, that period may be extended to 90 days.

Article 150

Request for additional information

The competent authority of the Member State may request the applicant to supply additional information on the particulars provided pursuant to Article 147 and on the qualified person referred to in Article 155.

Where the competent authority of the Member State requests additional information pursuant to the first subparagraph, the time limits referred to in Article 148(1), second subparagraph, and Article 149 shall be suspended until the additional information has been supplied.

Article 151

Obligations of the manufacturing authorisation holder

1. Member States shall ensure that manufacturing authorisation holders shall:

(a) have at their disposal the services of staff who comply with the legal requirements existing in the Member State both as regards manufacture and controls;

(b) dispose of the medicinal products only in accordance with the national legislation of the Member States;

(c) give prior notice to the competent authority of the Member State of any changes they wish to make to any of the particulars provided pursuant to Article 147;

(d) allow the competent authority of the Member State access to their premises at any time;

(e) enable the qualified persons referred to in Article 155 to carry out their duties, where applicable also in decentralised sites, for example by placing at their disposal all the necessary resources and ensuring their access to the premises, including relevant electronic systems and documentation of the decentralised site(s);

(f) comply, in any relevant site and at all times with the principles of good manufacturing practice for medicinal products referred to in Article 163;

(g) use only active substances that have been manufactured in accordance with the principles of good manufacturing practice for active substances referred to in Article 163 and distributed in accordance with the principles of good distribution practice for active substances referred to in Article 163;

(h) inform the competent authority of the Member State and the marketing authorisation holder immediately if they obtain information that medicinal products that come under the scope of their manufacturing authorisation are, or are suspected of, being, falsified irrespective of the way the medicinal products were distributed;

(i) verify that the manufacturers, importers or distributors from whom they obtain active substances are registered with the competent authority of the Member State in which they are established; and

(j) verify the authenticity and quality of the active substances and the excipients.

As regards the first subparagraph, point (c), the competent authority of the Member State shall, in any event, be immediately informed if the qualified person referred to in Article 155 is replaced unexpectedly.

For the purposes of the first subparagraph, points (f) and (g), manufacturing authorisation holders shall verify compliance by the manufacturer or distributors of active substances with the principles of good manufacturing and good distribution practices referred to in Article 163 by conducting regular audits at the manufacturing and distribution sites of the manufacturer and distributors of active substances. Manufacturing authorisation holders shall verify such compliance either by themselves or through an entity acting on their behalf under a contract.

2. The manufacturing authorisation holder shall ensure that the excipients are suitable for use in medicinal products by ascertaining the appropriate good manufacturing practice on the basis of a formalised risk assessment as referred to in Article 164.

3. The manufacturing authorisation holder shall ensure that the appropriate good manufacturing practice ascertained in accordance with paragraph 2 is applied. The manufacturing authorisation holder shall document the measures taken in accordance with paragraphs 1 and 2.

Article 152

Registration and supervision of decentralised sites

1. The manufacturing authorisation holder of the central site shall register all of its decentralised sites in accordance with this Article.

2. The manufacturing authorisation holder of the central site shall request the competent authority of the Member State in which the decentralised site is located to register the decentralised site.

3. For the purposes of paragraph 2, the manufacturing authorisation holder of the central site shall submit a registration form that includes the following information:

(a) name or corporate name and address of the decentralised site, a proof of its establishment in the Union and the name and contact details of a person designated as the local contact for the decentralised site and a written confirmation from the decentralised site that it supports the application for registration;

(b) the pharmaceutical forms and the medicinal products that are subject to manufacturing activities, including testing, in the decentralised site, the manufacturing activities, including testing, to be performed for those medicinal products and, where appropriate, the reference to the relevant marketing authorisation or marketing authorisation application referred to in Article 29;

(c) particulars regarding the premises of the decentralised site and the technical equipment to carry out the relevant activities;

(d) the reference to the manufacturing authorisation of the central site;

(e) the written confirmation by the qualified person referred to in Article 155 that the holder of a manufacturing authorisation for the medicinal product has verified compliance of the decentralised site with the principles of good manufacturing practice referred to in Article 163 by conducting audits, and when requested by the competent authority of the Member State in which the decentralised site is located, the latest audit report for the concerned decentralised site;

(f) proof that the appropriate resources are available at the central site for the qualified person referred to in Article 155 to carry out the tasks referred to in Article 157(4) regarding the supervision of the decentralised site.

4. The marketing authorisation holder shall ensure that all the activities at the central and decentralised sites are carried out in compliance with the principles of good manufacturing practice referred to in Articles 163 and 164 and the marketing authorisation referred to in Article 29.

5. The manufacturing authorisation holder of the central site shall not commence activities in a decentralised site until the use of decentralised manufacturing has been approved pursuant to Article 29(1) and the marketing authorisation holder has verified that:

(a) the corresponding central site is authorised by the competent authority of the Member State where it is located;

(b) the decentralised site is registered by the competent authority of the Member State where it is located; and

(c) in the Union database referred to in Article 191(15) a connection has been made between the registration of the decentralised site and the authorisation of the corresponding central site by the competent authority of the Member State where the central site is located.

6. The competent authority of the Member State where the decentralised site is located shall supervise, in accordance with Article 191, the manufacturing activities, including testing, carried out in the decentralised site.

7. The registration of a decentralised site shall include, where applicable, the registration of the site as a manufacturing site for the active substance pertaining to the medicinal product it encompasses.

8. When manufacturing activities at a decentralised site involve steps pertaining to the manufacture of the active substance of the medicinal product subject to decentralised manufacturing, those steps shall be included in the information submitted under paragraph 3, points (b), (c), (e) and (f).

9. The competent authority of the Member State supervising the decentralised site pursuant to paragraph 6 of this Article may carry out an inspection as referred to in Article 191(1), second subparagraph, point (a). In such cases, that competent authority shall cooperate with the competent authority of the Member State supervising the central site. If the outcome of the inspection shows that the applicant does not comply with the principles of good manufacturing practice referred to in Article 163, the competent authority of the Member State supervising the decentralised site shall not register that entity in the Union database referred to in Article 191(15) or, if that entity is already registered in the Union database referred to in Article 191(15), it shall remove the entity from that database.

10. The competent authority of the Member State supervising the decentralised site pursuant to paragraph 6 shall cooperate with the relevant authorities responsible for the supervision of manufacturing activities, including testing, under other Union acts as regards the medicinal products that were manufactured in a decentralised site, the testing or manufacturing of which involves using raw materials, medicinal products regulated under other relevant Union law or medicinal products that are intended to be combined with medical devices or *in vitro* diagnostic medical devices.

Where certain manufacturing activities, including testing, are carried out in relation to medicinal products containing, consisting of or derived from SoHO, for which certain manufacturing activities, including testing, are carried out within a decentralised site that is also authorised under Regulation (EU) 2024/1938, the cooperation referred to the first subparagraph shall include sharing information about any actions taken in relation to the decentralised site by the competent authorities concerned in carrying out their respective responsibilities.

The respective competent authorities of the Member States supervising the central and decentralised sites shall cooperate and exchange information as regards the authorisation of the central site, the registration of the decentralised sites and the supervision of those sites.

11. Where appropriate, the competent authorities of the Member States supervising the central and decentralised sites and the Agency or the competent authority of the Member State supervising the marketing authorisation shall cooperate and exchange information. Where they detect any deficiency in the central site or the decentralised sites that could impact the quality or safety of the medicinal product concerned, they shall inform the relevant competent authorities of the Member States or the Agency, as applicable, without undue delay.

12. Where a situation occurs which has an impact on the quality or safety of the medicinal products that are manufactured or tested at the decentralised site, the marketing authorisation holder and the qualified person of the central site shall inform the competent authorities of the Member States supervising the central and decentralised sites, and the competent authority of the Member State supervising the marketing authorisation or the Agency, as applicable, without undue delay, which shall take appropriate action.

13. The competent authority of the Member State supervising the decentralised site may suspend or revoke the registration of the decentralised site, fully or partially, as appropriate, if the conditions set out in paragraphs 2 to 7 of this Article cease to be met. In such an event that competent authority shall, without undue delay, inform all the competent authorities referred to in paragraph 11 and enter the information on the suspension or revocation in the Union database referred to in Article 191(15).

Article 153

Conditions related to the safety features

1. The safety features referred to in point (p) of Annex IV shall not be removed or covered, either fully or partially, unless the following conditions are fulfilled:

(a) the manufacturing authorisation holder has first verified that the medicinal product is authentic and has not been tampered with;

(b) the manufacturing authorisation holder complies with Annex IV by replacing those safety features, without opening the immediate packaging, with safety features that are equivalent;

(c) the replacement of the safety features is conducted in accordance with the principles of good manufacturing practice for medicinal products referred to in Article 163; and

(d) the replacement of the safety features is subject to supervision by the competent authority of the Member State.

For the purposes of point (b), safety features shall be considered to be equivalent to the original safety features if they:

(a) comply with the requirements set out in the delegated acts adopted pursuant to Article 70(2); and

(b) are equally effective in enabling the medicinal product to be identified, its authenticity to be verified and in providing evidence of tampering with the medicinal product.

2. Manufacturing authorisation holders, including those performing the activities referred to in paragraph 1, shall be regarded as manufacturers and therefore held liable for damages in the cases and under the conditions laid down in Directive (EU) 2024/2853.

Article 154

Potentially falsified medicinal products

1. By way of derogation from Article 1(2), and without prejudice to Chapter XII, Section 1, Member States shall take the necessary measures in order to prevent medicinal products that are introduced into the Union, but are not intended to be placed on the market in the Union, from entering into circulation on the Union market if there are sufficient grounds to suspect that those products are falsified.

2. Member States shall communicate public information on the actions they have taken to prevent and combat the falsification of medicinal products, including enforcement measures. For that purpose, they shall involve patients' and consumers' organisations and, where necessary, Member States' enforcement authorities.

3. In order to establish what the necessary measures referred to in paragraph 1 of this Article are, the Commission is empowered to adopt delegated acts in accordance with Article 218, to supplement paragraph 1 of this Article by specifying the criteria to be considered and the verifications to be made when assessing the potential falsified character of medicinal products introduced into the Union but not intended to be placed on the market.

Article 155

Availability of the qualified person

1. Member States shall take all appropriate measures to ensure that the manufacturing authorisation holder has permanently and continuously at its disposal the services of at least one qualified person in accordance with the conditions laid down in Article 156, who resides and operates in the Union and who is responsible, in particular, for carrying out the duties specified in Article 157.

2. A manufacturing authorisation holder who is a natural person and personally fulfils the conditions of qualification set out in Annex III may assume the responsibility referred to in paragraph 1.

3. Where the manufacturing authorisation is granted to a central site specified in the application pursuant to Article 148, the qualified person referred to in paragraph 1 of this Article shall also be responsible for carrying out the duties specified in Article 157(4) regarding the decentralised sites. For those purposes, the available resources for the services referred to in paragraph 1 of this Article at a central site shall be commensurate with the number of decentralised sites and the activities carried out at those sites.

Article 156

Qualification of the qualified person

1. Member States shall ensure that the qualified person referred to in Article 155 fulfils the conditions of qualification set out in Annex III.

2. The manufacturing authorisation holder and the qualified person shall ensure that the practical experience acquired by the qualified person is appropriate to the types of products to be certified.

3. The competent authority of the Member State may establish appropriate administrative procedures to verify that the qualified person referred to in Article 155 fulfils the conditions set out in Annex III.

Article 157

Responsibilities of the qualified person

1. Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 155, without prejudice to its relationship with the manufacturing authorisation holder, is responsible, subject to the procedures referred to in Article 158, for securing:

   (a) in the case of medicinal products manufactured within the Member State concerned, that each production batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorisation;

(b) in the case of medicinal products imported from third countries, irrespective of whether they have been manufactured in the Union, that each production batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of the medicinal products in accordance with the requirements of the marketing authorisation.

The qualified person referred to in Article 155 shall, in the case of medicinal products intended to be placed on the Union market, ensure that the safety features referred to in point (p) of Annex IV have been affixed on the packaging.

The batches of medicinal products that have undergone the controls referred to in the first subparagraph, point (b), in a Member State shall be exempt from those controls if they are marketed in another Member State, accompanied by the control reports signed by the qualified person.

2. In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Union with the exporting country to ensure that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Union, and to ensure that the controls referred to in paragraph 1, first subparagraph, point (b), have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls.

3. In all cases and particularly where the medicinal products are released for sale, the qualified person shall certify in a register or equivalent format provided for that purpose, that each production batch satisfies the provisions of this Article; that register or equivalent format shall be kept up to date during the time when operations are carried out and shall remain at the disposal of the competent authority of the Member State for the period specified in the national law of the Member State concerned and in any event for at least five years.

4. For the purposes of Article 155(3), the qualified person shall, in addition:

(a) supervise the manufacturing activities, including testing, carried out at the decentralised sites to ensure that they comply with the principles of good manufacturing practice referred to in Article 163 and conform to the marketing authorisation;

(b) conduct regular audits, including periodic on-site visits, at the decentralised sites and provide a written confirmation that the holder of the manufacturing authorisation for the central site has verified compliance of the decentralised site with the principles of good manufacturing practice referred to in Article 163;

(c) notify annually to the competent authority of the Member State where the decentralised site is located, an inventory of the changes that have taken place as regards the information provided in the registration form submitted pursuant to Article 152(3).

Any changes that may have an impact on the quality or safety of the medicinal products that are manufactured or tested at the decentralised site must be notified immediately.

The Commission is empowered to adopt a delegated act in accordance with Article 218 to supplement the first subparagraph, point (c), specifying the notification made by the qualified person.

Article 158

Professional code of conduct

1. Member States shall ensure that the duties of the qualified persons referred to in Article 155 are fulfilled, either by means of appropriate administrative measures or by making such persons subject to a professional code of conduct.

2. Member States may provide for the temporary suspension of a qualified person referred to in Article 155 upon the commencement of administrative or disciplinary procedures against that qualified person for failure to fulfil its duties set out in Article 157. The suspension of a qualified person applies to all manufacturing authorisations concerned.

3. In the case of decentralised manufacturing, the competent authorities of the Member States supervising the central site and the decentralised sites, if different, shall cooperate to implement the measures referred to in paragraphs 1 and 2.

Article 159

Certificates for a medicinal product intended for export

1. At the request of the manufacturer, the exporter or the competent authorities of an importing third country, the competent authority of the Member State shall issue a certificate for export to certify that a manufacturer of medicinal products is in possession of a manufacturing authorisation or refer to the manufacturing authorisation and the certificate of compliance with good manufacturing practice (GMP certificate) available in the Union database referred to in Article 191(15).

2. For the purposes of paragraph 1, when the manufacturer is not in possession of a marketing authorisation it shall provide the competent authority of the Member State responsible for issuing the certificate referred to in paragraph 1, with a declaration explaining why a marketing authorisation is not available.

3. At the request of a marketing authorisation holder or a marketing authorisation applicant, the competent authority of the Member State or the Agency, as applicable, shall issue a certificate for the medicinal product in compliance with the applicable administrative arrangements of the World Health Organization.

4. For the purposes of paragraph 3 of this Article, the competent authority of the Member State or the Agency, as applicable, shall, for medicinal products intended for export that are already authorised in their territory, supply the summary of product characteristics as approved by them in accordance with Article 46 or, as appropriate, refer to the summary of product characteristics they made publicly available.

SECTION 2

MANUFACTURING, IMPORT AND DISTRIBUTION OF ACTIVE SUBSTANCES

Article 160

Registration of importers, manufacturers and distributors of active substances

1. Importers, manufacturers and distributors of active substances who are established in the Union shall register their activity with the competent authority of the Member State in which they are established.

2. Importers, manufacturers and distributors of active substances referred to in paragraph 1 shall apply for registration by submitting electronically a registration form to the competent authority of the Member State at least 60 days prior to the intended commencement of their activity. Member States may, until … [seven years from the date of entry into force of this Directive] allow registration forms to be submitted in paper format.

3. The registration form shall include, at least, the following information:

   (a) name or corporate name and permanent address;

   (b) the active substances that are to be imported, manufactured or distributed;

   (c) particulars regarding the premises and the technical equipment for their activity.

4. The competent authority of the Member State may, based on a risk assessment, decide to carry out an inspection. If the competent authority of the Member State notifies the applicant for registration within 60 days of the receipt of the registration form that an inspection will be carried out, the activity shall not begin before the competent authority of the Member State has notified the applicant for registration that they may commence the activity. If within 60 days of the receipt of the registration form the competent authority of the Member State has not notified the applicant for registration that an inspection will be carried out, the applicant may commence the activity.

5. If the outcome of the inspection carried out in accordance with paragraph 4 of this Article shows that the applicant for registration does not comply with the principles of good manufacturing or good distribution practices for active substances referred to in Article 163, the competent authority shall not register that entity in the Union database referred to in Article 191(15).

6. Annually, importers, manufacturers and distributors of active substances referred to in paragraph 1 shall communicate electronically to the competent authority of the Member State an inventory of the changes that have taken place as regards the information provided in the registration form referred to in paragraph 3. Any changes that may have an impact on the quality or safety of the active substances that are manufactured, imported or distributed must be notified immediately.

7. The competent authority of the Member State shall enter the information provided pursuant to paragraph 3 of this Article in the Union database referred to in Article 191(15).

8. The competent authority of the Member State may suspend or revoke the registration of the entity fully or partially, as appropriate, if the conditions set out in paragraph 3 of this Article and Article 161 cease to be met. In such an event the competent authority of the Member State shall without undue delay inform the competent authorities of other Member States and the Agency and enter the information on the suspension or revocation in the Union database referred to in Article 191(15).

Article 161

Conditions for importing active substances

1. Member States shall take appropriate measures to ensure that the manufacture, import and distribution on their territory of active substances, including active substances that are intended for export, comply with the principles of good manufacturing and good distribution practices for active substances referred to in Article 163.

2. Active substances shall only be imported if the following conditions are fulfilled:

   (a) the active substances have been manufactured in accordance with principles of good manufacturing practice at least equivalent to those referred to in Article 163; and

   (b) the active substances are accompanied by a written confirmation issued by the competent authority of the exporting third country stating that:

      (i) the principles of good manufacturing practice applicable to the manufacturing site manufacturing the exported active substance are at least equivalent to those referred to in Article 163;

(ii) the manufacturing site concerned is subject to regular, strict and transparent controls and to the effective enforcement of good manufacturing practice, including repeated and unannounced inspections, so as to ensure a protection of public health at least equivalent to that in the Union; and

(iii) in the event of findings relating to non-compliance, information on such findings is supplied by the exporting third country to the Union without undue delay.

3. The conditions set out in paragraph 2, point (b), of this Article shall not apply if the exporting country is included in the list referred to in Article 162(2).

4. The conditions set out in paragraph 2, point (b), of this Article may be waived by any competent authority of a Member State for a period not exceeding the validity of the certificate of compliance with good manufacturing practice issued in accordance with Article 191(13) where a site manufacturing an active substance for export has been inspected by the competent authority of a Member State or the Agency and was found to comply with the principles of good manufacturing practice referred to in Article 163.

Article 162

Active substances imported from third countries

1. At the request of a third country, the Commission shall assess whether the third country's regulatory framework applicable to active substances exported to the Union and the respective control and enforcement activities ensure a level of protection of public health equivalent to that of the Union.

   The assessment shall take the form of a review of relevant documentation submitted electronically and, unless arrangements as referred to in Article 157(2) are in place that cover this area of activity, that assessment shall include an on-site review of the third country's regulatory system and, if necessary, an observed inspection of one or more of the third country's manufacturing sites for active substances.

2. Based on the assessment referred to in paragraph 1 of this Article, the Commission may adopt implementing acts to include the third country in a list and to apply the requirements set out in the second subparagraph of this paragraph. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 217(2).

   When assessing the third country's regulatory framework pursuant to paragraph 1, the Commission shall take account of the following:

   (a) the third country's rules for good manufacturing practice;

   (b) the regularity of inspections to verify compliance with good manufacturing practice;

(c) the effectiveness of enforcement of good manufacturing practice;

(d) the regularity and rapidity of information provided by the third country relating to non-compliant manufacturers of active substances.

3. The Commission shall verify regularly whether the conditions laid down in paragraph 1 are fulfilled. The first verification shall take place no later than three years after the third country has been included in the list referred to in paragraph 2.

4. The Commission shall perform the assessment referred to in paragraph 1 and verification referred to in paragraph 3 in cooperation with the Agency and the competent authorities of the Member States.

SECTION 3

PRINCIPLES OF GOOD MANUFACTURING AND GOOD DISTRIBUTION PRACTICES

Article 163

Rules applicable to medicinal products and active substances

The Commission shall adopt delegated acts in accordance with Article 218 to supplement this Directive by specifying:

(a) the principles of good manufacturing and good distribution practices for medicinal products complemented, where relevant, by specific measures applicable in particular to pharmaceutical forms, medicinal products or manufacturing activities in line with good manufacturing principles;

(b) the principles of good manufacturing and good distribution practices for active substances.

The principles to be specified under the first paragraph, point (a), shall include specific provisions for brokering.

Where relevant, the principles to be specified under the first paragraph shall be consistent with other principles of good practice established under any other Union legal framework.

The Agency, in particular through its inspection working group referred to in Article 148, point (k), of Regulation (EU) 2026/…[+], in agreement with the Commission, shall draw up guidelines on good manufacturing and distribution practices, including guidelines specific to ATMPs.

Article 164

Rules applicable to excipients

The Commission is empowered to adopt delegated acts in accordance with Article 218 to supplement this Directive as regards the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients referred to in Article 151(2). Such risk assessment shall take into account requirements under other appropriate quality systems as well as the source and intended use of the excipients and previous instances of quality defects.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

Chapter XII

Wholesale distribution and sale at a distance

SECTION 1

WHOLESALE DISTRIBUTION AND BROKERING OF MEDICINAL PRODUCTS

Article 165

Wholesale distribution of medicinal products

1. Without prejudice to Article 6, Member States shall take all appropriate action to ensure that only medicinal products in respect of which a marketing authorisation has been granted in accordance with Union law are distributed on their territory.

2. In the case of wholesale distribution including storage, medicinal products shall be covered by either a centralised marketing authorisation or by a national marketing authorisation.

3. Wholesale distributors who intend to obtain a medicinal product from a Member State ('source Member State') shall notify the marketing authorisation holder and the competent authority of the Member State in which the medicinal product is to be distributed ('destination Member State') of their intention to distribute that medicinal product in the destination Member State.

4. Member States shall ensure that the wholesale distributor demonstrates that the medicinal product obtained from a source Member State and distributed in the destination Member State is already covered by a marketing authorisation in the destination Member State, including that the medicinal products share a common origin. A Member State may set additional requirements whose fulfilment it considers necessary to demonstrate that the medicinal product authorised in the source Member State and the medicinal product authorised in the destination Member State can be reasonably considered to be the same product.

The destination Member State shall refuse to permit the parallel trade of a medicinal product by a wholesale distributor from the source Member State where the destination Member State considers that permitting such parallel trade would circumvent the mutual recognition procedure as laid down in Article 39.

5. In the case of medicinal products covered by a national marketing authorisation, the notification referred to in paragraph 3 of this Article to the competent authority of the destination Member State shall be without prejudice to additional procedures provided for in the national legislation of that Member State and to fees payable to that competent authority for examining the notification. A Member State may require that the medicinal product concerned is labelled in accordance with Article 77. The Member State may also require that the electronic product information is provided in accordance with Article 66(3).

6. In the case of medicinal products covered by a centralised marketing authorisation, the wholesale distributor shall submit the same notification referred to in paragraph 3 to the Agency, which will be in charge of checking that the conditions laid down in Union law on medicinal products and in the marketing authorisations are observed. For this check, a fee shall be payable to the Agency.

Article 166

Authorisation for wholesale distribution of medicinal products

1. Each Member State shall take all appropriate measures to ensure that the wholesale distribution of medicinal products on its territory is subject to authorisation ('wholesale distribution authorisation'). The wholesale distribution authorisation shall indicate the premises, the categories of medicinal products and the wholesale distribution operations for which it is valid.

2. Where persons authorised or entitled to supply medicinal products to the public may also, under national law, engage in wholesale distribution of medicinal products, such persons shall be subject to the authorisation provided for in paragraph 1.

3. A manufacturing authorisation granted pursuant to Article 148 shall include an authorisation for the wholesale distribution of the medicinal products that are covered by the manufacturing authorisation. A wholesale distribution authorisation shall not give rise to an exemption from the obligations set out in Article 146 to hold a manufacturing authorisation or to comply with any conditions set out therein, even where the manufacturing or import activities are secondary to the wholesale distribution activities.

4. The competent authority of the Member State shall enter the information relating to the wholesale distribution authorisations in the Union database referred to in Article 191(15).

5. Where the competent authority of a Member State grants a wholesale distribution authorisation, it shall ensure that controls in relation to the persons authorised to engage in wholesale distribution of medicinal products, and inspections of their premises, are carried out at an appropriate frequency.

It may suspend or revoke the wholesale distribution authorisation if the conditions set out in Articles 165 and 167 cease to be met, or if the obligations set out in Article 169 are no longer fulfilled. In such event the Member State shall, without undue delay, inform the other Member States and the Commission thereof.

6. Where the competent authority of the Member State considers that the conditions for granting a wholesale distribution authorisation set out in Articles 165 and 167 are not met and the obligations set out in Article 169 are not fulfilled with respect to a wholesale distribution authorisation granted by the competent authority of another Member State, it shall without undue delay inform the Commission and the competent authority of the other Member State thereof. The competent authority of the other Member State shall take the measures it considers necessary and shall inform the Commission and the competent authority of the first Member State of those measures and the reasons for them.

Article 167

Application for a wholesale distribution authorisation

1. In order to obtain a wholesale distribution authorisation, applicants shall submit an application electronically to the competent authority of the Member State. Member States may until … [seven years from the date of entry into force of this Directive] allow applications to be submitted in paper format.

2. The application referred to in paragraph 1 shall include the following particulars:

   (a) confirmation and proof that the applicants have a permanent address in the Member State and have at their disposal suitable and adequate premises, installations and equipment, to ensure proper conservation and distribution of the medicinal products;

   (b) confirmation and proof that the applicants have at their disposal appropriately trained staff, and in particular a responsible person, meeting the qualifications and conditions provided for by the national legislation of the Member State;

   (c) an undertaking by the applicants to fulfil the obligations incumbent on them under the terms of Article 169.

Article 168

Granting of a wholesale distribution authorisation

1. The competent authority of the Member State shall carry out an inspection to confirm the accuracy of the particulars included in the application submitted in accordance with Article 167.

   Where the accuracy of the particulars is confirmed in accordance with the first subparagraph, or in any event, no later than 90 days of the receipt of the application submitted in accordance with Article 167 the competent authority of the Member State shall grant or refuse a wholesale distribution authorisation.

   By way of derogation from the second subparagraph, in justified cases, the inspection may be carried out after the wholesale distribution authorisation has been granted.

2. The competent authority of the Member State may require the applicant to supply, electronically, any additional information on the particulars that is necessary for granting the wholesale distribution authorisation. In such case, the period laid down in paragraph 1 shall be suspended until the requisite additional information is supplied.

3. Member States may until … [seven years from the date of entry into force of this Directive] allow the information referred to in paragraph 2 to be submitted in paper format.

4. The competent authority of the Member State may grant a wholesale distribution authorisation subject to conditions.

5. The wholesale distribution authorisation shall apply only to the wholesale distribution activities, categories of medicinal products and the premises specified in the authorisation.

Article 169

Obligations of the wholesale distribution authorisation holder

1. Member States shall ensure that wholesale distribution authorisation holders are required to:

(a) have at their disposal the services of staff who comply with the legal requirements existing in the Member State as regards wholesale distribution;

(b) allow the competent authority of the Member State access to their premises, installations and equipment referred to in Article 167(2), point (a), at all times;

(c) procure, including by financial transactions, their supplies of medicinal products only from persons who are themselves in possession of a wholesale distribution authorisation in the Union or a manufacturing authorisation referred to in Article 166(3);

(d) supply, including by financial transaction, medicinal products only to persons who are themselves wholesale distribution authorisation holders or who are authorised or entitled to supply medicinal products to the public;

(e) verify that the medicinal products received are not falsified by checking the safety features on the outer packaging, in accordance with the requirements laid down in the delegated acts adopted pursuant to Article 70(2), second subparagraph;

(f) have an emergency plan that ensures effective implementation of any recall from the market ordered by the competent authorities of the Member States or the Commission, as applicable, or carried out in cooperation with the manufacturer or the marketing authorisation holder for the medicinal product concerned;

(g) keep records giving, for any medicinal products received, dispatched or brokered, at least the following information:

(i) the date of receipt, dispatch or brokering of the medicinal product;

(ii) the name of the medicinal product;

(iii) the quantity of the medicinal product received, supplied or brokered;

(iv) the name and address of the supplier of the medicinal product or the consignee, as appropriate;

(v) the batch number of the medicinal products, at least for medicinal products bearing the safety features referred to in Article 70;

(h) keep the records referred to in point (g) available to the competent authorities of the Member States, for supervision purposes, for a period of five years;

(i) comply with the principles of good distribution practice for medicinal products referred to in Article 163;

(j) maintain a quality system setting out responsibilities, processes and risk management measures in relation to their activities;

(k) immediately inform the competent authority of the Member State and, where applicable, the marketing authorisation holder, of medicinal products they receive or are offered that they identify as falsified or suspect to be falsified;

(l) continuously guarantee, within the limits of their responsibility, the appropriate and continued supply of a suitable range of medicinal products to meet the requirements of a specific geographical area, and deliver the supplies requested over the whole of the area in question, within a reasonable timeframe in accordance with the requirements of the national legislation;

(m) cooperate with marketing authorisation holders, competent authorities of the Member States and the Agency on the security of supply measures referred to in Chapter X of Regulation (EU) 2026/…[+];

(n) cooperate with marketing authorisation holders and competent authorities of the Member States on monitoring and management of shortages and critical shortages referred to in Chapter X of Regulation (EU) 2026/…[+].

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

2. Where the medicinal product is obtained from another wholesale distributor, the wholesale distribution authorisation holders obtaining the product shall verify compliance with the principles of good distribution practice by the supplying wholesale distributor. This includes verifying whether the supplying wholesale distributor holds a wholesale distribution authorisation, or a manufacturing authorisation referred to in Article 166(3).

3. Where the medicinal product is obtained from a manufacturer or importer, wholesale distribution authorisation holders shall verify that the manufacturer or importer holds a manufacturing authorisation.

4. Where the medicinal product is obtained through brokering of medicinal products, wholesale distribution authorisation holders shall verify that the person brokering the medicinal product fulfils the requirements set out in Article 174.

5. In respect of a medicinal product for which the regulatory market protection referred to in Article 83(2) of this Directive or the extension of market exclusivity referred to in Article 74(1) of Regulation (EU) 2026/…[+] does not apply in a Member State pursuant to Article 59(5) of this Directive, the wholesale distribution authorisation holder or any person or entity engaged in sale at a distance of medicinal products shall not make the generic, biosimilar, hybrid or bio-hybrid medicinal product available on the market of another Member State where the regulatory market protection referred to in Article 83(2) of this Directive and, if applicable, the extension of market exclusivity referred to in Article 74(1) of Regulation (EU) 2026/…[+] apply, during the regulatory market protection period or market exclusivity period.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

Where such a generic, biosimilar, hybrid or bio-hybrid medicinal product is intended for export to a Member State in which the regulatory market protection and market exclusivity periods do not apply pursuant to Article 59(5) of this Directive, the wholesale distribution authorisation holder shall keep specific records available to the competent authorities of the Member States for a period of three years.

Article 170

Obligation of supply of medicinal products

1. With regard to the supply of medicinal products to pharmacists and other persons authorised or entitled to supply medicinal products to the public, Member States shall not impose upon the holder of a wholesale distribution authorisation that has been granted by another Member State any obligation, in particular public service obligations, more stringent than those they impose on persons whom they have themselves authorised to engage in equivalent activities.

2. The wholesale distributors of a medicinal product placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacists and other persons authorised or entitled to supply medicinal products to the public so that the needs of patients in the Member State in question are met.

3. The arrangements for implementing this Article shall, moreover, be justified on grounds of public health protection and be proportionate in relation to the objective of such protection, in compliance with the TFEU, particularly as regards the free movement of goods and competition.

Article 171

Documentation accompanying supplied medicinal products

1. For all supplies of medicinal products to a person authorised or entitled to supply medicinal products to the public in the Member State concerned, the holder of a wholesale distribution authorisation shall provide a document, which may be submitted in electronic format, that makes it possible to ascertain the following:

   (a) the date of the supply;

   (b) the name and pharmaceutical form of the medicinal product;

   (c) the quantity of the medicinal product supplied;

   (d) the name and address of the supplier of the medicinal product and consignee;

   (e) the batch number of the medicinal products, at least for medicinal products bearing the safety features referred to in Article 70.

2. Member States shall take all appropriate measures to ensure that persons authorised or entitled to supply medicinal products to the public are able to provide information that makes it possible to trace the distribution path of every medicinal product.

Article 172

National requirements for wholesale distribution

This Chapter shall not prevent the application of more stringent requirements laid down by Member States in respect of the wholesale distribution of:

(a) narcotic or psychotropic substances;

(b) medicinal products derived from blood;

(c) immunological medicinal products; and

(d) radiopharmaceuticals.

Article 173

Wholesale distribution to third countries

In the case of wholesale distribution of medicinal products to third countries, Article 165 and Article 169(1), point (d), shall not apply.

Where wholesale distributors supply medicinal products to persons in third countries, they shall ensure that such supplies are only made to persons who are authorised or entitled to receive medicinal products for wholesale distribution or supply to the public in accordance with the applicable legal and administrative provisions of the third country concerned.

Article 171 shall apply to the supply of medicinal products to persons in third countries authorised or entitled to supply medicinal products to the public.

Article 174

Brokering medicinal products

1. Persons brokering medicinal products shall ensure that the brokered medicinal products are covered by a valid marketing authorisation granted in accordance with Union law.

   Persons brokering medicinal products shall have a permanent address and contact details in the Union, so as to ensure accurate identification, location, communication and supervision of their activities by the competent authorities of the Member States.

   The requirements set out in Article 169(1), points (f) to (k), shall apply *mutatis mutandis* to the brokering of medicinal products.

2. Persons may only broker medicinal products if they are registered with the competent authority of the Member State where they have their permanent address referred to in paragraph 1, second subparagraph. Those persons shall submit, electronically, at least, their name, corporate name and permanent address to the competent authority of the Member State in order to register. They shall notify, electronically, the competent authority of the Member State of any changes thereof without undue delay.

   Member States may until … [seven years from the date of entry into force of this Directive] allow for the information referred to in the first subparagraph to be submitted in paper format.

   The competent authority of the Member State shall enter the information referred to in the first subparagraph in a register that shall be publicly available.

3. Inspections referred to in Article 191 shall be carried out under the responsibility of the Member State where the person brokering medicinal products is registered.

If a person brokering medicinal products does not comply with the requirements set out in this Article, the competent authority of the Member State may decide to remove that person from the register referred to in paragraph 2. In such event, the competent authority of the Member State shall notify that person thereof.

SECTION 2

SALE AT A DISTANCE TO THE PUBLIC

Article 175

General requirements for sale at a distance

1. Without prejudice to national legislation prohibiting the offer of medicinal products subject to medical prescription for sale at a distance to the public by means of information society services, Member States shall ensure that the offer of medicinal products for sale at a distance to the public by means of services as defined in Directive (EU) 2015/1535 of the European Parliament and of the Council[54] is subject to the following conditions:

(a) the natural or legal person offering the medicinal products is authorised or entitled to supply medicinal products to the public, also at a distance, in accordance with national legislation of the Member State in which that person is established;

[54] Directive (EU) 2015/1535 of the European Parliament and of the Council of 9 September 2015 laying down a procedure for the provision of information in the field of technical regulations and of rules on Information Society services (OJ L 241, 17.9.2015, p. 1, ELI: http://data.europa.eu/eli/dir/2015/1535/oj).

(b) the person referred to in point (a) has notified the Member State in which that person is established of at least the following information:

(i) name or corporate name and permanent address of the place of activity from where those medicinal products are supplied;

(ii) the starting date of the activity of offering medicinal products for sale at a distance to the public by means of information society services;

(iii) the address of the website used for that purpose and all relevant information necessary to identify that website;

(iv) if applicable, the prescription status in accordance with Chapter IV of the medicinal products offered for sale at a distance to the public by means of information society services;

(c) the medicinal products comply with the national legislation of the Member State of destination in accordance with Article 6(1);

(d) without prejudice to the information requirements set out in Directive 2000/31/EC of the European Parliament and of the Council[55], the website offering the medicinal products for sale at a distance to the public contains at least:

(i) the contact details of the competent authority of the Member State or the authority notified pursuant to point (b);

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[55] Directive 2000/31/EC of the European Parliament and of the Council of 8 June 2000 on certain legal aspects of information society services, in particular electronic commerce, in the Internal Market (Directive on electronic commerce) (OJ L 178, 17.7.2000, p. 1, ELI: http://data.europa.eu/eli/dir/2000/31/oj).

(ii) a hyperlink to the website referred to in Article 177 of the Member State of establishment;

(iii) the common logo referred to in Article 176 clearly displayed on every page of the website that relates to the offer for sale at a distance to the public of medicinal products.

Where appropriate, the information referred to in the first subparagraph, point (b), shall be updated.

The common logo referred to in the first subparagraph, point (d)(iii), shall contain a hyperlink to the entry of the person in the list referred to in Article 177(1), point (c).

2. Member States may impose conditions, where justified on grounds of public health protection, for the retail supply on their territory of medicinal products for sale at a distance to the public by means of information society services.

3. Without prejudice to Directive 2000/31/EC and the requirements set out in this Section, Member States shall take the necessary measures to ensure that persons other than those referred to in paragraph 1 that offer medicinal products for sale at a distance to the public by means of information society services and that operate on their territory are subject to effective, proportionate and dissuasive penalties.

Article 176

Requirements for common logo

1. A common logo shall be established that is recognisable throughout the Union, while enabling the identification of the Member State where the person offering medicinal products for sale at a distance to the public is established. That logo shall be clearly displayed on websites offering medicinal products for sale at a distance to the public in accordance with Article 175(1), point (d).

2. In order to harmonise the functioning of the common logo, the Commission shall adopt implementing acts regarding:

   (a) the technical, electronic and cryptographic requirements for verification of the authenticity of the common logo;

   (b) the design of the common logo.

   Those implementing acts shall, where necessary, be amended to take account of technical and scientific progress. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 217(2).

Article 177

Information about sale at a distance to the public

1. Each Member State shall set up a website providing at least the following:

(a) information on the national legislation applicable to the offering of medicinal products for sale at a distance to the public by means of information society services, including information on the fact that there may be differences between Member States regarding classification of medicinal products and the conditions for their supply;

(b) information on the purpose of the common logo;

(c) the list of persons offering the medicinal products for sale at a distance to the public in that Member State by means of information society services in accordance with Article 175 as well as their website addresses;

(d) background information on the risks related to medicinal products supplied illegally to the public by means of information society services.

The website referred to in the first subparagraph shall contain a hyperlink to the website referred to in paragraph 2.

2. The Agency shall set up a website providing the information referred to in paragraph 1, first subparagraph, points (b) and (d), information on Union law applicable to falsified medicinal products as well as hyperlinks to the Member States' websites referred to in paragraph 1. The Agency's website shall explicitly mention that the Member States' websites contain information on persons authorised or entitled to supply medicinal products for sale at a distance in the Member State concerned.

3. The Commission shall, in cooperation with the competent authorities of the Member States or the Agency, as applicable, conduct or promote information campaigns aimed at the general public on the dangers of falsified medicinal products. Those campaigns shall raise consumer awareness of the risks related to medicinal products supplied illegally for sale at a distance as well as of the functioning of the common logo and the websites referred to in paragraphs 1 and 2.

Chapter XIII
Advertising

Article 178

Definition of advertising of medicinal products

1. For the purposes of this Chapter, ‘advertising of medicinal products’ includes any form of information activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products.

   It includes in particular:

   (a) the advertising of medicinal products to the general public;

   (b) the advertising of medicinal products to persons qualified to prescribe, administer or supply them, referred to in this Chapter as healthcare professionals;

   (c) visits by medical sales representatives to healthcare professionals;

   (d) the supply of samples of medicinal products free of charge;

   (e) the provision of inducements to prescribe or supply medicinal products by the gift, offer or promise of any benefit or bonus, whether in money or in kind;

(f) the sponsorship of promotional meetings attended by healthcare professionals;

(g) the sponsorship of, or any form of financial contribution for, scientific events attended by healthcare professionals, including payments to the organising entity and payment of participants' travel, accommodation and catering expenses in connection with such events;

(h) advertising related to medicinal products that does not refer to specific medicinal products.

2. This Chapter does not cover:

(a) labelling and package leaflets, which are subject to Chapter VI;

(b) correspondence, whether or not accompanied by material of a non-promotional nature, needed to answer a specific question about a particular medicinal product, provided it does not promote the prescription or consumption of the medicinal product;

(c) factual, informative announcements and reference material relating, for example, to pack changes, adverse-reaction warnings as part of general drug precautions, trade catalogues and price lists, provided they include no product claims;

(d) information relating to human health or diseases, provided that there is no reference, even indirect, to medicinal products.

Article 179

General provisions on advertising of medicinal products

1. Member States shall prohibit any advertising of a medicinal product in respect of which a marketing authorisation has not been granted.

2. All parts of the advertising of a medicinal product shall be in accordance with the particulars listed in the summary of product characteristics.

3. The advertising of a medicinal product shall:

   (a) encourage the rational use of the medicinal product, by presenting it objectively and without exaggerating its properties;

   (b) be accurate, verifiable and not be misleading;

   (c) not induce an excessive or abusive use of the medicinal product.

4. Any form of advertising that aims to highlight negatively another medicinal product shall be prohibited. Advertising that suggests that a medicinal product is safer or more effective than another medicinal product shall also be prohibited, unless the comparison of quality, safety or efficacy is supported objectively by the summaries of product characteristics.

Article 180

Restrictions on advertising of medicinal products

1. Member States shall prohibit the advertising to the general public of medicinal products that:

   (a) are subject to medical prescription, in accordance with Chapter IV;

   (b) contain substances classified as psychotropic or narcotic substances within the meaning of international conventions.

2. Medicinal products may be advertised to the general public where, by virtue of their composition and purpose, they are intended and designed for use without the intervention of a healthcare professional for diagnostic purposes or for the prescription or monitoring of treatment, with the advice of the pharmacist, if necessary.

3. Member States may prohibit, on their territory:

   (a) advertising to the general public of medicinal products the cost of which may be reimbursed;

   (b) advertising related to medicinal products that does not refer to a specific medicinal product.

4. The prohibition contained in paragraph 1 shall not apply to campaigns promoting vaccination where those campaigns are carried out or approved by the Member States.

5. The prohibition referred to in paragraph 1 shall apply without prejudice to Article 21 of Directive 2010/13/EU.

6. Member States shall prohibit the direct distribution of medicinal products to the public by the industry for promotional purposes.

7. Member States may suspend the advertising of a medicinal product in the case of shortages or risk of shortage of that medicinal product. The suspension shall be withdrawn as soon as the shortage or risk of shortage ceases.

8. Member States may apply stricter measures with regard to the advertising of medicinal products to healthcare professionals qualified to administer medicinal products.

Article 181

Advertising to the general public

1. Without prejudice to Article 180, all advertising to the general public of a medicinal product shall:

   (a) be set out in such a way that it is clear that the message is an advertisement and that the product is clearly identified as a medicinal product; and

   (b) include, as a minimum, the following information:

      (i) the name of the medicinal product, as well as the common name if the medicinal product contains only one active substance;

(ii) the information necessary for correct use and disposal of the medicinal product;

(iii) an express, legible invitation to read carefully the instructions on the package leaflet or on the outer packaging, as the case may be, and to consult a medical practitioner or a pharmacist for additional information.

2. Member States may decide that the advertising of a medicinal product to the general public may, notwithstanding paragraph 1, include only the name of the medicinal product or its active substance, or the trademark if it is intended solely as a reminder.

Article 182

Restrictions on advertising to the general public

1. The advertising of a medicinal product to the general public shall not contain any material that:

(a) gives the impression that a medical consultation or surgical operation is unnecessary, in particular by offering a diagnosis or by suggesting treatment by any means of communication;

(b) suggests that the effects of taking the medicinal product are guaranteed, are unaccompanied by adverse reactions or are better than, or equivalent to, those of another treatment or medicinal product;

(c) suggests that the health of the subject can be enhanced by taking the medicinal product;

(d) suggests that the health of the subject could be affected by not taking the medicinal product;

(e) is directed exclusively or principally at children;

(f) refers directly or indirectly to a recommendation by scientists, healthcare professionals, healthcare facilities or persons who are none of the foregoing but who, because of their celebrity or professional activity, could encourage the consumption of medicinal products;

(g) suggests that the medicinal product is a food, cosmetic or other consumer product;

(h) suggests that the safety or efficacy of the medicinal product is due to the fact that it is of natural origin;

(i) could, by a description or detailed representation of a case history, lead to erroneous self-diagnosis;

(j) refers, in improper, alarming or misleading terms, to claims of recovery;

(k) uses, in improper, alarming or misleading terms, pictorial representations of changes in the human body caused by disease or injury, or of the action of a medicinal product on the human body or parts thereof.

2. The prohibition contained in paragraph 1, point (d), of this Article shall not apply to the campaigns promoting vaccination referred to in Article 180(4).

Article 183

Advertising to healthcare professionals

1. The advertising of a medicinal product to healthcare professionals shall include both of the following:

   (a) essential information compatible with the summary of product characteristics;

   (b) the prescription status of the medicinal product.

   Member States may also require such advertising to include the selling price or indicative price of the various presentations and the conditions for reimbursement.

2. Member States may decide that the advertising of a medicinal product to healthcare professionals may, notwithstanding paragraph 1, include only the name of the medicinal product, or its international non-proprietary name, where this exists, or the trademark, if it is intended solely as a reminder.

Article 184

Supporting documentation for advertising to healthcare professionals

1. Any documentation relating to a medicinal product that is transmitted as part of the promotion of that medicinal product to persons qualified to prescribe, administer or supply it shall include, as a minimum, the particulars listed in Article 183(1) and shall state the date on which it was drawn up or last revised.

2. All the information contained in the documentation referred to in paragraph 1 shall be accurate, up-to-date, verifiable and sufficiently complete to enable the recipient to form its own opinion of the therapeutic value of the medicinal product concerned.

3. Quotations as well as tables and other illustrative matter taken from medical journals or other scientific works for use in the documentation referred to in paragraph 1 shall be faithfully reproduced and the precise sources indicated.

Article 185

Obligations related to medical sales representatives

1. Medical sales representatives shall be given adequate training by their employer and shall have sufficient scientific knowledge to be able to provide information that is precise and as complete as possible about the medicinal products that they promote. The information provided by medical sales representatives shall be in accordance with Article 179.

2. During each visit, medical sales representatives shall give the persons visited, or have available for them, summaries of the product characteristics of each medicinal product they present together with, if the legislation of the Member State so permits, details of the price and conditions for reimbursement referred to in Article 183(1), second subparagraph.

3. Medical sales representatives shall transmit to the scientific service referred to in Article 190(1) any information about the use of the medicinal products they advertise, with particular reference to any adverse reactions reported to them by the persons they visit.

Article 186

Promotion of medicinal products

1. Where medicinal products are being promoted to healthcare professionals, no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to such persons.

2. Paragraph 1 shall not prevent hospitality being offered at promotional events. Such hospitality shall always be strictly limited to the main purpose of the event. The hospitality must not be extended to persons other than healthcare professionals.

3. Healthcare professionals shall not solicit or accept any inducement prohibited under paragraph 1 or contrary to paragraph 2.

4. Existing measures or trade practices in Member States relating to prices, margins and discounts shall not be affected by paragraphs 1, 2 and 3.

Article 187

Hospitality at scientific events

Article 186(1) shall not prevent hospitality being offered, directly or indirectly, at events for purely professional and scientific purposes. Such hospitality shall be strictly limited to the main scientific objective of the event and shall be inexpensive. The hospitality shall not be extended to persons other than healthcare professionals.

Article 188

Provision of samples of medicinal products free of charge

1. Samples of medicinal products shall be provided free of charge on an exceptional basis only to persons qualified to prescribe them and on the following conditions:

   (a) the number of samples for each medicinal product each year on prescription shall be limited;

   (b) any supply of samples shall be in response to a written request, signed and dated, from the persons qualified to prescribe or supply medicinal products;

   (c) the persons who supply samples shall maintain an adequate system of control and accountability;

   (d) each sample shall be no larger than the smallest presentation on the market;

   (e) each sample shall be marked ‘free medical sample – not for sale’ or shall show some other wording having the same meaning;

(f) each sample shall be accompanied by a copy of the summary of product characteristics;

(g) no samples of medicinal products containing substances classified as psychotropic or narcotic substances within the meaning of international conventions or antibiotic may be supplied.

2. Member States may decide that on an exceptional basis, free samples of medicinal products not subject to medical prescription may also be provided to persons qualified to supply them, subject to the conditions of paragraph 1.

3. Member States may also place further restrictions on the distribution of samples of certain medicinal products free of charge.

Article 189

Implementation of advertising provisions by the Member States

1. Member States shall ensure that there are adequate and effective methods to monitor the advertising of medicinal products. Such methods, which may be based on a system of prior vetting, shall in any event include legal provisions under which persons or organisations regarded under national law as having a legitimate interest in prohibiting any advertisement inconsistent with this Chapter, may take legal action against such advertisement, or bring such advertisement before the competent authority of the Member State either to decide on complaints or to initiate appropriate legal proceedings.

2. Under the legal provisions referred to in paragraph 1, Member States shall confer upon the courts or competent authorities of the Member States powers enabling them, in cases where they deem such measures to be necessary, taking into account all the interests involved, and in particular the public interest:

(a) to order the cessation of, or to institute appropriate legal proceedings for an order for the cessation of, misleading advertising; or

(b) if misleading advertising has not yet been published but publication is imminent, to order the prohibition of, or to institute appropriate legal proceedings for an order for the prohibition of, such publication.

Member States shall confer upon the courts or competent authorities of the Member States the powers referred to in the first subparagraph, points (a) and (b), even without proof of actual loss or damage or of intention or negligence on the part of the advertiser.

3. Member States shall make provision for the measures referred to in paragraph 2 to be taken under an accelerated procedure, either with interim effect or with definitive effect.

It shall be for each Member State to decide which of the two options set out in the first subparagraph to select.

4. Member States may confer upon the courts or competent authorities of the Member States powers enabling them, with a view to eliminating the continuing effects of misleading advertising the cessation of which has been ordered by a final decision:

(a) to require publication of that decision in full or in part and in such form as they deem adequate;

(b) to require in addition the publication of a corrective statement.

5. In the absence of national rules governing the disclosure of transfers of value, Member States shall establish and maintain on the national medicines web portal referred to in Article 105 a publicly available list of links to the disclosure platforms operated by trade associations or by marketing authorisation holders for the reporting of transfers of value related to the advertising activities referred to in Articles 185 to 188, as applicable. Marketing authorisation holders shall provide the necessary weblinks and shall remain responsible for ensuring the accuracy and timely publication of the disclosed information.

6. Paragraphs 1 to 4 shall not exclude the voluntary control of advertising of medicinal products by self-regulatory bodies and recourse to such bodies, if proceedings before such bodies are possible in addition to the judicial or administrative proceedings referred to in paragraph 1.

Article 190

Implementation of advertising provisions by the marketing authorisation holder

1. The marketing authorisation holders shall establish, within their organisation, a scientific service in charge of information about the medicinal products that they place on the market.

2. The marketing authorisation holder shall:

   (a) keep available for, or communicate to, the competent authorities of the Member States or bodies responsible for monitoring advertising of medicinal products, a sample of all advertisements emanating from its undertaking or not-for-profit entities together with a statement indicating the persons to whom it is addressed, the method of dissemination and the date of first dissemination;

   (b) ensure that advertising of medicinal products by their undertaking or not-for-profit entities conforms to the requirements of this Chapter;

   (c) verify that medical sales representatives employed by their undertaking or not-for-profit entities have been adequately trained and fulfil the obligations imposed upon them by Article 185, paragraphs 2 and 3;

   (d) supply the competent authorities of the Member States or bodies responsible for monitoring advertising of medicinal products with the information and assistance they require to carry out their responsibilities;

(e) ensure that the decisions taken by the competent authorities of the Member States or bodies responsible for monitoring advertising of medicinal products are immediately and fully complied with.

3. Member States shall not prohibit the co-promotion of a medicinal product by the marketing authorisation holders and one or more companies nominated by them.

Chapter XIV
Supervision and controls

SECTION 1
SUPERVISION

Article 191
System of supervision and inspections

1. The competent authority of the Member State concerned shall, in cooperation with the Agency and where relevant, other Member States, ensure compliance with this Directive, including the principles of good manufacturing and good distribution practices referred to in Articles 163 and 164.

For the purposes of the first subparagraph, the competent authority of the Member State shall have in place a system of supervision that shall include the following measures:

(a) announced and, where appropriate, unannounced on-site inspections;

(b) remote inspections, where justified;

(c) compliance control measures;

(d) the effective follow-up of the measures referred to in points (a), (b) and (c).

2. The competent authority of the Member State and the Agency shall exchange information on the inspections referred to in paragraph 1, second subparagraph, points (a) and (b), that are planned or that have been conducted and shall cooperate in the coordination of such inspections.

3. The competent authority of the Member State shall ensure that the measures referred to in paragraph 1, second subparagraph, are carried out by the official representatives of the competent authority of the Member State concerned, at an appropriate frequency to be determined by a risk-based approach, at the premises or in respect of the activities of the following:

(a) manufacturers of medicinal products located in the Union or in third countries, including where appropriate at central or decentralised sites, and wholesale distributors of medicinal products located in the Union;

(b) manufacturers of active substances located in the Union or in third countries and importers and distributors of active substances located in the Union.

4. To implement the risk-based approach referred to in paragraph 3, the competent authority of the Member State may:

(a) rely on inspection reports from trusted non-Union regulatory authorities;

(b) take into account whether the manufacturer of active substance is located in a third country included in the list referred to in Article 162(2).

5. Where the competent authority of the Member State considers it necessary, including where there are grounds for suspecting non-compliance with this Directive, including with the principles of good manufacturing and good distribution practices referred to in Articles 163 and 164, it may have its official representatives carry out the measures referred to in paragraph 1, second subparagraph, of this Article at the premises or in respect of the activities of the following:

(a) applicants for a manufacturing authorisation or wholesale distribution authorisation for medicinal products;

(b) applicants for registration of manufacturing, import and distribution of active substances;

(c) decentralised sites subject to a request for a registration and registered decentralised sites;

(d) marketing authorisation holders;

(e) without prejudice to paragraph 3, manufacturers and wholesale distributors of medicinal products, manufacturers and distributors of active substances located in the Union or in third countries and importers of medicinal products or active substances located in the Union;

(f) manufacturers of excipients, functional excipients, starting materials or intermediate products located in the territory of the Member State concerned or in a third country;

(g) importers of excipients, functional excipients, starting materials or intermediate products located in the territory of the Member State concerned;

(h) persons brokering medicinal products located in the territory of the Member State concerned;

(i) third parties, contracted by the marketing authorisation holder or a marketing authorisation applicant for the performance of certain of its tasks or the preparation of evidence or data submitted in accordance with Annex II.

6. The measures referred to in paragraph 1, second subparagraph, may also be carried out at the request of a competent authority of a Member State, the Commission or the Agency in the Union or in third countries or, where appropriate, by asking an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose to carry out tests on samples.

7. Each Member State shall ensure that official representatives of its competent authorities are empowered and required to carry out one or more of the following activities:

(a) inspect the manufacturing or commercial establishments of manufacturers of medicinal products, of active substances or of excipients, and any laboratories employed by the manufacturing authorisation holder to carry out verifications and controls pursuant to Article 9;

(b) examine any documents and records to verify compliance with this Directive, and obtain evidence, such as copies of documents, photographs or videos;

(c) take samples during an inspection or request samples as part of the measures referred to in paragraph 1, second subparagraph, including any required essential testing material or reagent with a view to independent tests being carried out by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose;

(d) inspect the premises, records, documents and pharmacovigilance system master file of the marketing authorisation holder or any undertaking employed by the marketing authorisation holder to perform the activities described in Chapter IX.

8. Inspections referred to in paragraph 1, second subparagraph, points (a) and (b), of this Article shall be carried out in accordance with the principles referred to in Article 193.

9. After every inspection carried out in accordance with paragraphs 3 and 5 of this Article, the competent authority of the Member State concerned shall issue a report on the compliance of the activities inspected with the principles of good manufacturing and good distribution practices referred to in Articles 163 and 164, as applicable.

10. The competent authority of the Member State that had its official representatives carry out inspections in accordance with paragraphs 3 and 5, shall share its preliminary report with the inspected entity.

11. Before adopting the report, the competent authority of the Member State shall give the inspected entity the opportunity to submit comments.

12. Without prejudice to any arrangements that may have been concluded between the Union and third countries, a Member State, the Commission or the Agency may require a manufacturer of a medicinal product or of an active substance established in a third country to submit to an inspection as referred to in this Article.

13. Within 90 days of an inspection being carried out in accordance with paragraphs 3 and 5 of this Article, the competent authority of the Member State concerned shall issue the inspected entity with a certificate of compliance with good manufacturing practice or good distribution practice if the outcome of that inspection shows that the inspected entity complies with the principles of good manufacturing or good distribution practices referred to in Articles 163 and 164.

14. If the outcome of the inspection carried out in accordance with paragraph 3 and 5 of this Article shows that the inspected entity does not comply with the principles of good manufacturing or good distribution practices referred to in Articles 163 and 164, the competent authority of the Member State concerned shall issue a statement of non-compliance, and shall revoke the certificate of compliance with good manufacturing practice or good distribution practice fully or partially, as appropriate.

15. The competent authority of the Member State shall enter the certificates of compliance with good manufacturing practice or good distribution practice in the relevant Union database managed by the Agency on behalf of the Union. The competent authority of the Member State shall also enter information in that database regarding the registration of decentralised sites performing decentralised manufacturing activities and of importers, manufacturers and distributors of active substances pursuant to Article 152(5), points (b) and (c), Article 152(9) and (13) and Article 160(7) and (8), respectively.

16. If the outcome of the inspection carried out in accordance with paragraph 3 and 5 of this Article is that the inspected entity does not comply with the legal requirements or the principles of good manufacturing or good distribution practices as referred to in Articles 163 and 164 the information shall be entered in the Union database as referred to in paragraph 15 of this Article, as appropriate.

17. If the outcome of the activity carried out in accordance with paragraph 7, point (d), is that the marketing authorisation holder does not comply with the pharmacovigilance system as described in the pharmacovigilance system master file and with Chapter IX, the competent authority of the Member State concerned shall bring the deficiencies to the attention of the marketing authorisation holder and give the marketing authorisation holder the opportunity to submit comments.

In such cases, the Member State concerned shall inform the other Member States, the Agency and the Commission accordingly.

Where appropriate, the Member State concerned shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties as laid down in Article 209.

Article 192

Cooperation on inspections

1. Upon request by one or more competent authorities of the Member States, inspections referred to in Article 191(3) and (5) of this Directive may be carried out by official representatives from more than one Member State, together with the inspectors of the Agency if specifically requested by those competent authorities of the Member States in accordance with Article 54(1) of Regulation (EU) 2026/…[+] (the 'joint inspection').

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

The competent authority of the Member State receiving a request for a joint inspection shall make all reasonable efforts, taking into account their available resources, to accept such a request and to coordinate and support that joint inspection, where:

(a) it is demonstrated, or there are reasonable ground for suspecting, that the activities carried out on the territory of the Member State receiving the request pose a risk to the safety and quality of the medicinal product in the Member State of the competent authority requesting the joint inspection and the competent authorities of the Member States concerned agree that an inspection is needed;

(b) the competent authority of the Member State requesting the joint inspection requires specialist technical expertise available in the Member State receiving the request;

(c) the competent authority of the Member State receiving the request agrees that there are other reasonable grounds, such as training of inspectors or sharing of good practice, for conducting a joint inspection.

2. The competent authorities of the Member States participating in a joint inspection, and the Agency, as applicable, shall conclude an agreement prior to the inspection that specifies at least the following:

(a) the scope and objective of the joint inspection;

(b) the roles of the participating inspectors during and following the inspection, including the designation of an authority leading the inspection;

(c) the powers and responsibilities of each of the competent authorities.

Where the joint inspection is conducted on the territory of one of the Member States, the competent authority of that Member State shall act as the leading authority for the joint inspection, unless otherwise agreed between the Member States.

3. The competent authorities of the Member States participating in the joint inspection, and the Agency, as applicable, shall commit themselves in that agreement to jointly accept the results of the inspection.

4. Where the joint inspection is conducted in one of the Member States, the competent authority of that Member State shall ensure that the joint inspection is carried out in accordance with the national legislation of the Member State in which the joint inspection takes place.

5. Member States may set up joint inspection programmes to facilitate routine joint inspections. Member States may operate such programmes under an agreement as referred to in paragraphs 2 and 3.

6. A competent authority of a Member State may request the competent authority of another Member State to take over responsibility for conducting one of its inspections referred to in Article 191, paragraphs 3 and 5.

7. Within 10 days of receipt of a request pursuant to paragraph 6, the competent authority which has received the request shall communicate to the requesting competent authority whether it accepts the request to conduct the inspection. Where it accepts the request, it shall be the competent authority responsible for conducting the inspection pursuant to this Section.

8. For the purposes of paragraph 6, and if the request is accepted, the requesting competent authority shall, in a timely manner, submit the relevant information necessary to conduct the inspection to the competent authority of the Member State that accepted the request.

Article 193

Principles applicable to supervision and inspections

1. The Commission shall adopt delegated acts in accordance with Article 218 to supplement this Directive by laying down the principles applicable to:

(a) the system of supervision referred to in Article 191(1);

(b) the joint inspections referred to in Article 192(1);

(c) the exchange of information and cooperation in the coordination of inspections in the system of supervision between the Member States and the Agency referred to in Article 191(2);

(d) the trusted non-Union regulatory authorities referred to in Article 191(4), point (a); and

(e) the exchange of information and cooperation as regards decentralised manufacturing between the competent authorities of the Member States supervising the central site and decentralised sites and the competent authority of the Member State supervising the marketing authorisation or the Agency, as applicable, referred to in Article 152(11).

2. Member States shall, in cooperation with the Agency, establish the form and content of the manufacturing authorisation referred to in Article 146(1), the wholesale distribution authorisation referred to in Article 166(1), the report referred to in Article 191(9), the certificate of compliance with good manufacturing practice and the certificate of compliance with good distribution practice referred to in Article 191(13) and the statement of non-compliance referred to in Article 191(14).

SECTION 2

CONTROLS

Article 194

Controls on medicinal products

Member States shall take all appropriate measures to ensure that the marketing authorisation holder and, where appropriate, the holder of a manufacturing authorisation for a medicinal product provide proof of the controls carried out in accordance with the methods laid down in Annex II on the medicinal product or the ingredients and of the controls carried out at an intermediate stage of the manufacturing process.

Article 195

Submission of control reports for immunological medicinal products and for medicinal products derived from human blood or plasma

For the purpose of implementing Article 194, Member States may require manufacturers of immunological medicinal products and of medicinal products derived from human blood or plasma to submit to a competent authority of the Member States copies of all the control reports signed by the qualified person in accordance with Article 157.

Article 196

Batch control of specific medicinal products by Member States

1. Where it considers it necessary in the interests of public health, a Member State may require the submission of samples from each batch of the medicinal product and, if necessary, from the bulk, for examination by an Official Medicines Control Laboratory, or a laboratory that the Member State has designated for that purpose, before release onto the market, by the marketing authorisation holders for the following medicinal products:

   (a) live vaccines;

   (b) immunological medicinal products used in the primary immunisation of infants or of other groups at risk;

   (c) immunological medicinal products used in public health immunisation programmes;

(d) new immunological medicinal products or immunological medicinal products manufactured using new or altered kinds of technology or new for a particular manufacturer, during a transitional period normally specified in the marketing authorisation.

However, where another Member State has previously examined a batch of the medicinal product and declared it to be in conformity with the approved specifications, the Member State referred to in the first subparagraph shall not require the holder of a marketing authorisation for that medicinal product to submit samples from that batch. In such a case, the declaration of conformity issued by that other Member State shall be recognised by the Member State referred to in the first subparagraph.

The marketing authorisation holder, in consultation with the Official Medicines Control Laboratory, shall make reasonable efforts to submit samples for the examination referred to in the first subparagraph at the beginning of its own controls. Member States shall ensure that any such examination is completed within 30 days of the receipt of both the samples and the documentation of the controls carried out by the marketing authorisation holder in accordance with Article 194. That period shall be extended to 60 days if necessary to complete the examination.

2. Where, in the interests of public health, the national law of a Member State so provides, the competent authorities of the Member State may require the marketing authorisation holder for medicinal products derived from human blood or human plasma to submit samples from each batch of the medicinal product and if required, from the bulk, for examination by an Official Medicines Control Laboratory, or a laboratory that a Member State has designated for that purpose, before release onto the market, unless the competent authorities of another Member State have previously examined the batch in question and declared it to be in conformity with the approved specifications, in which case, the declaration of conformity issued by that other Member State shall be recognised.

The marketing authorisation holder, in consultation with the Official Medicines Control Laboratory, shall make reasonable efforts to submit samples for the examination referred to in the first subparagraph at the beginning of its own controls. Member States shall ensure that any such examination is completed within 30 days of the receipt of both the samples and the documentation of the controls carried out by the marketing authorisation holder in accordance with Article 194. That period shall be extended to 60 days if necessary to complete the examination.

Article 197

Processes for the preparation of medicinal products derived from substances of human origin

1. Member States shall take all necessary measures to ensure that the manufacturing and purifying processes used in the preparation of medicinal products derived from substances of human origin are, insofar as the state of technology permits, properly validated, attain batch-to-batch consistency and guarantee the absence of specific viral or other adventitious agent contamination.

2. For the purposes of paragraph 1, manufacturers shall notify the competent authorities of the Member States of the methods used to reduce or eliminate pathogenic virus or other adventitious agents liable to be transmitted by medicinal products derived from substances of human origin. The competent authority of the Member State may submit samples of the medicinal product and from the bulk if required, for testing by a State laboratory or a laboratory designated for that purpose, either during the examination of the application pursuant to Article 32, or after a marketing authorisation has been granted.

Chapter XV

Restrictions of marketing authorisations

Article 198

Suspension, revocation or variation of marketing authorisations

1. The competent authorities of the Member States or, in the case of centralised marketing authorisation, the Commission, shall suspend, revoke or vary a marketing authorisation if the view is taken that the medicinal product is harmful, that it lacks therapeutic efficacy that the benefit-risk balance is not favourable or that its qualitative and quantitative composition is not as declared. Therapeutic efficacy shall be considered to be lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.

2. The competent authorities of the Member States or, in the case of centralised marketing authorisation, the Commission, may suspend, revoke or vary a marketing authorisation if a serious risk to the environment or public health has been identified and not sufficiently addressed by the marketing authorisation holder.

3. A marketing authorisation may also be suspended, revoked or varied where the particulars and documents supporting the application as provided for in Articles 7 and 10 to 15 or Annexes I to V are incorrect or have not been amended in accordance with Article 92, or where any conditions referred to in Articles 47, 48 and 89 of this Directive or Articles 19, 20 and 21 of Regulation (EU) 2026/…[+] have not been fulfilled or where the controls referred to in Article 194 have not been carried out.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

4. Paragraph 3 shall also apply in cases where the manufacture of the medicinal product is not carried out in compliance with the particulars provided pursuant to Annex I, or where controls are not carried out in compliance with the control methods laid down in Annex II.

5. The competent authorities of the Member States or, in the case of centralised marketing authorisation, the Commission may suspend or revoke the marketing authorisation for a category of preparations or all preparations where any of the requirements laid down in Article 147 is no longer met.

Article 199

Prohibition of supply or withdrawal of a medicinal product from the market

1. Without prejudice to the measures provided for in Article 198, the competent authorities of the Member States and, in the case of centralised marketing authorisation, the Commission shall take all appropriate steps to ensure that the supply of the medicinal product is prohibited and the medicinal product withdrawn from the market, if the view is taken that:

   (a) the medicinal product is harmful;

   (b) the medicinal product lacks therapeutic efficacy;

   (c) the benefit-risk balance is not favourable;

   (d) the qualitative and quantitative composition of the medicinal product is not as declared;

(e) the controls required pursuant to Article 194 have not been carried out;

(f) some other requirement or obligation relating to the granting of the manufacturing authorisation for the medicinal product has not been fulfilled; or

(g) a serious risk to the environment or to public health due to the release of the medicinal product into the environment has been identified and has not been sufficiently addressed by the marketing authorisation holder.

2. The competent authorities of the Member States or, in the case of centralised marketing authorisation, the Commission, may limit the prohibition to supply the product, or its withdrawal from the market, to those batches that are the subject of dispute.

3. The competent authorities of the Member States or, in the case of centralised marketing authorisation, the Commission, may, for a medicinal product for which the supply has been prohibited or that has been withdrawn from the market in accordance with paragraphs 1 and 2, in exceptional circumstances during a transitional period allow the supply of the medicinal product to patients who are already being treated with the medicinal product.

Article 200

Suspected falsified medicinal products and medicinal products with suspected quality defects

1. Member States shall have a system in place that aims at preventing medicinal products that are suspected to present a danger to health from reaching the patient.

2. The system referred to in paragraph 1 shall cover the receipt and handling of notifications of suspected falsified medicinal products as well as of medicinal products with suspected quality defects. The system shall also cover recalls of medicinal products by marketing authorisation holders and withdrawals of medicinal products from the market ordered by competent authorities of the Member States or, in the case of centralised marketing authorisation, by the Commission from all relevant actors in the supply chain both during and outside normal working hours. The system shall also make it possible to recall, where necessary with the assistance of health professionals, medicinal products from patients who received such products.

3. If the medicinal product in question is suspected of presenting a serious risk to public health, the competent authority of the Member State in which that product was first identified shall, without undue delay, transmit a rapid alert notification to all Member States and all actors in the supply chain in that Member State. In the event of such medicinal products being deemed to have reached patients, urgent public announcements shall be issued within 24 hours in order to recall those medicinal products from the patients. Those announcements shall contain sufficient information on the suspected quality defect or falsification and the risks involved.

Article 201

Suspending or revoking a manufacturing authorisation or imports from third countries

In addition to the measures specified in Article 199, the competent authority of the Member State may suspend the manufacture of medicinal products or imports of medicinal products from third countries, or suspend or revoke the manufacturing authorisation for a category of preparations or all preparations where Articles 148, 151, 157 and 194 are not complied with.

Article 202

Refusal, suspension or revocation within the limits of this Directive

1. A marketing authorisation for a medicinal product shall not be refused, suspended or revoked except on the grounds set out in this Directive.

2. No decision concerning suspension of manufacture or of imports of medicinal products from third countries, prohibition of supply or withdrawal from the market of a medicinal product may be taken except on the grounds set out in Article 198(5) and Articles 199 and 201.

Chapter XVI
General provisions

Article 203

Competent authorities of the Member States

1. Member States shall designate the competent authorities to carry out tasks under this Directive.

2. Member States shall ensure that adequate financial resources are available to provide the staff and other resources necessary for the competent authorities to carry out the activities required by this Directive and Regulation (EU) 2026/…[+].

3. The competent authorities of the Member States shall cooperate with each other and with the Agency and the Commission in the performance of their tasks under this Directive and Regulation (EU) 2026/…[+] to ensure proper application and due enforcement. The competent authorities of the Member States shall communicate to each other all appropriate information within a reasonable timeframe.

4. The competent authorities of the Member States may process personal health data from clinical trials and other sources, including real world data, to support their public health tasks and, in particular, the evaluation and monitoring of medicinal products, for the purposes of improving the robustness of the scientific assessment or verifying claims of the applicant or marketing authorisation holder.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

Processing of personal data under this Directive shall be subject to Regulations (EU) 2016/679 and (EU) 2018/1725.

Article 204

Cooperation with other authorities

1. Member States, in implementing this Directive, shall ensure that when questions arise with regard to the regulatory status of a medicinal product, in relation to their link to substances of human origin as referred to in Regulation (EU) 2024/1938, the competent authorities of the Member States consult the Agency and the relevant authorities established under that Regulation.

2. Member States, in implementing this Directive, shall take the necessary measures to ensure cooperation between competent authorities responsible for medicinal products and customs authorities.

3. In order to improve regulatory certainty and cross-sectoral cooperation, Member States and the Agency may request the Commission, where necessary, to organise joint meetings between the Agency and the relevant advisory and regulatory bodies established under other Union legal acts to assess, for the purposes of this Directive, emerging trends and questions on the regulatory status of products or substances and to find agreement on common regulatory status principles. The summaries and conclusions of those joint meetings shall be made publicly available, including the opinions and conclusions of each of the respective bodies. The Commission may also organise such joint meetings on its own initiative.

Article 205

Member States exchange of information on manufacturing or wholesale distribution authorisations for medicinal products

1. Member States shall take all appropriate measures to ensure that the competent authorities of the Member States concerned communicate to each other such information as is appropriate to guarantee that the requirements placed on the authorisations referred to in Articles 146 and 166, on the certificates referred to in Article 191(13) or on the marketing authorisations are fulfilled.

2. Upon reasoned request, Member States shall send electronically the report referred to in Article 191(9) to the competent authorities of another Member State or to the Agency.

3. The conclusions reached in accordance with Article 191(13) or (14) shall be valid throughout the Union.

4. However, in exceptional cases, if a Member State is unable, for reasons relating to public health, to accept the conclusions reached following an inspection under Article 191(1), that Member State shall without undue delay inform the Commission and the Agency. The Agency shall inform the Member States concerned.

5. When the Commission is informed of these divergences of opinion, it may, after consulting the Member States concerned, ask the inspector who performed the original inspection to perform a new inspection; the inspector may be accompanied by two other inspectors from Member States that are not parties to the disagreement.

Article 206

Information on prohibition of supply or other action relating to a marketing authorisation

1. Each Member State shall take all the appropriate measures to ensure that decisions granting a marketing authorisation, refusing or revoking a marketing authorisation, withdrawing a decision refusing or revoking a marketing authorisation, prohibiting supply, or withdrawing a product from the market, together with the reasons on which such decisions are based, are brought to the attention of the Agency without undue delay.

2. The marketing authorisation holder shall notify the competent authority of the Member State without undue delay of any action it takes to suspend the marketing of a medicinal product, to withdraw a medicinal product from the market, to request the withdrawal of a marketing authorisation or not to apply for the renewal of a marketing authorisation, together with the reasons for such action.

The marketing authorisation holder shall declare whether the action referred to in the first subparagraph of this paragraph is based on any of the grounds set out in Article 198 or 199(1) and specify the grounds for such action.

3. The marketing authorisation holder shall also make the notification referred to in paragraph 2 of this Article in cases where the action is taken in a third country and where such action is based on any of the grounds set out in Article 198 or 199(1).

4. The marketing authorisation holder shall also notify the Agency where the action referred to in paragraph 2 or 3 of this Article is based on any of the grounds set out in Article 198 or 199(1).

5. The marketing authorisation holder shall make the notifications referred to in this Article electronically, in the formats made available by the Agency. The Agency shall consult the Member States when drawing up the formats.

6. The Agency shall forward notifications received in accordance with paragraph 4 to all Member States without undue delay.

7. Member States shall ensure that appropriate information about action taken pursuant to paragraphs 1 and 2 that could affect the protection of public health in third countries is brought to the attention of the World Health Organization without undue delay and that a copy of that information is sent to the Agency.

8. Each year, the Agency shall make public a list of the medicinal products for which marketing authorisations have been refused, revoked or suspended in the Union, or that have been withdrawn from the market, or the supply of which has been prohibited, including the reasons for such action.

Article 207

Notification of decisions

1. Any decision referred to in this Directive that is taken by the competent authority of a Member State shall state in detail the reasons on which it is based.

2. Any such decision shall be notified to the party concerned, together with information as to the redress available to them under the laws in force and of the time limit allowed for access to such redress.

3. Decisions to grant or revoke a marketing authorisation shall be made publicly available.

Article 208

Authorisation of a medicinal product on public health grounds

1. In the absence of a marketing authorisation or where there is no marketing authorisation application pending for a medicinal product authorised in another Member State in accordance with Chapter III, a Member State may, where justified on public health reasons, such as the need to ensure access, availability or security of supply of that medicinal product, authorise the placing on the market of that medicinal product.

2. When a Member State avails itself of the possibility set out in paragraph 1, it shall adopt the necessary measures in order to ensure that the requirements of this Directive are complied with, in particular those referred to in Chapters IV, VI, IX, XIII and XIV, and Article 209. Member States may decide to exempt medicinal products authorised under paragraph 1 from the requirements laid down in Article 77(1) and (2).

3. Before granting a marketing authorisation under paragraph 1, a Member State:

   (a) shall notify the marketing authorisation holder, in the Member State in which the medicinal product concerned is authorised, of the proposal to grant a marketing authorisation under this Article in respect of the medicinal product concerned;

(b) may request the competent authority of the Member State referred to in point (a) to submit copies of the assessment report referred to in Article 46(3) and of the marketing authorisation in force in respect of the medicinal product concerned. If so requested, the competent authority of that Member State shall supply, within 30 days of receipt of the request, a copy of the assessment report and the marketing authorisation in respect of the medicinal product concerned.

4. The Commission shall set up a publicly available register of medicinal products authorised under paragraph 1. Member States shall notify the Commission if any medicinal product is authorised, or ceases to be authorised, under paragraph 1, including the name or corporate name and permanent address of the marketing authorisation holder.

The Commission shall amend the register of medicinal products referred to in the first subparagraph accordingly and make that register available on its website.

Article 209

Penalties

1. Member States shall lay down the rules on penalties applicable to infringements of national provisions adopted pursuant to this Directive and shall take all measures necessary to ensure that they are implemented. The penalties provided for shall be effective, proportionate and dissuasive. Member States shall, without delay, notify the Commission of those rules and of those measures and shall notify it, without delay, of any subsequent amendment affecting them.

Those penalties shall not be inferior to those applicable to infringements of national law of similar nature and importance.

2. The rules referred to in paragraph 1, first subparagraph, shall address, inter alia, the following:

(a) the manufacture, distribution, brokering, import and export of falsified medicinal products, as well as sale at distance of falsified medicinal products to the public;

(b) non-compliance with the provisions laid down in this Directive on manufacturing, distribution, import and export of active substances;

(c) non-compliance with the provisions laid down in this Directive on the use of excipients;

(d) non-compliance with the provisions laid down in this Directive on pharmacovigilance;

(e) non-compliance with the provisions laid down in this Directive on advertising.

3. Where relevant, the penalties shall take into account the risk to public health presented by the falsification of medicinal products.

Article 210

Collection and management of unused or expired medicinal products

Member States shall ensure that an appropriate and accessible collection system is in place for medicinal products that are unused or have expired and that the collected medicinal products are managed properly in accordance with applicable Union and national environmental law, taking into account best available techniques.

Article 211

Re-dispensing to the public of unused medicinal products

1. A medicinal product collected in accordance with Article 210 shall not be re-dispensed to patients.

2. By way of derogation from paragraph 1, Member States may allow specific unused medicinal products that are subject to medical prescription and have already been dispensed to patients, to be collected and re-dispensed by a pharmacy to patients served by that pharmacy if all of the following conditions are met:

   (a) the medicinal product is collected and re-dispensed by the same pharmacy that initially dispensed it;

   (b) the pharmacy is, at its own request, authorised by the competent authority of the Member State to re-dispense medicinal products;

(c) the collection of the unused medicinal product is not prejudicial to the patient to whom it was initially dispensed;

(d) the collected medicinal product has not already been the subject of re-dispensation;

(e) the medicinal product was initially dispensed with a view to being potentially re-dispensed and necessary safeguards were applied by the dispensing pharmacy to ensure that the medicinal product would not be tampered with and its storage and transport conditions would be respected;

(f) the re-dispensed medicinal product is intended for use by an individual patient, identified by name;

(g) after having been informed by the pharmacy of the use of a re-dispensed medicinal product and the rules concerning re-dispensing under applicable national laws in accordance with this Article, the patient referred to in point (f) has given explicit consent in writing to be supplied with the re-dispensed medicinal product.

3. Member States shall ensure that before a pharmacy re-dispenses medicinal products to patients in accordance with paragraph 2, the pharmacy:

(a) verifies that the medicinal product concerned is not a falsified medicinal product;

(b) verifies that the expiry date of the medicinal product has not passed and that the medicinal product has been stored and transported under appropriate conditions;

(c) records the name and the batch number of the medicinal product, the name of the patient from whom the medicinal product has been collected and the name of the receiving patient for the purpose of recall, investigations and supervision.

4. Member States may set additional restrictive conditions under which medicinal products can be re-dispensed to patients in their territory.

5. Member States shall ensure that the collection and re-dispensing of medicinal products is not used for obtaining economic gain and that the re-dispensed medicinal products do not re-enter the supply chain.

6. Member States shall lay down rules on liability for potential harm resulting from the use of the medicinal products that have been re-dispensed where such harm results from a failure to ensure appropriate storage or transport conditions between the initial dispensing and the return of the medicinal product to the pharmacy, or a failure to ensure that the medicinal product re-dispensed has not been falsified.

7. The information on the safety features contained in the repositories system referred to in Article 70(2), point (e), shall not be modified upon collection or re-dispensing of a medicinal product.

8. This Article shall not apply to medicinal products that are offered for sale at a distance.

9. Member States shall notify to the Commission the national rules they implement within the scope of this Article. In particular, Member States shall notify:

(a) the types of medicinal products for which re-dispensing is allowed in accordance with this Article;

(b) the categories of pharmacies entitled to re-dispense medicinal products;

(c) the additional safety measures and the additional restrictive conditions introduced in accordance with paragraph 2, point (e), and paragraph 4.

Article 212

Declaration of interests

1. In order to guarantee independence and transparency, Member States shall ensure that members of staff of their competent authority responsible for granting authorisations, rapporteurs and experts concerned with the authorisation and surveillance of medicinal products have no direct or indirect financial or other interests in the pharmaceutical industry that could affect their impartiality and their independence.

Members of staff of the competent authority responsible for granting authorisations, rapporteurs and experts concerned with the authorisation and surveillance of medicinal products shall make an annual declaration of their financial interests and update that declaration whenever necessary.

2. In addition, Member States shall ensure that their competent authority makes publicly available its rules of procedure and those of its medicinal products' authorisation committees, agendas for its meetings and records of its meetings, accompanied by decisions taken, including minority opinions.

Chapter XVII
Specific provisions concerning the United Kingdom in respect of Northern Ireland

Article 213

Provisions relevant to the United Kingdom in respect of Northern Ireland

1. By way of derogation from Article 58(7), marketing authorisations may be granted by the competent authorities of the United Kingdom in respect of Northern Ireland:

   (a) to marketing authorisation applicants established in parts of the United Kingdom other than Northern Ireland;

   (b) to marketing authorisation holders established in parts of the United Kingdom other than Northern Ireland, in accordance with the mutual recognition procedure or the decentralised procedure laid down in Chapter III, Sections 3 and 4.

The competent authorities of the United Kingdom in respect of Northern Ireland may extend marketing authorisations already granted prior to 20 April 2022 to marketing authorisation holders established in parts of the United Kingdom other than Northern Ireland.

2. By way of derogation from Article 32(7) and (8), Article 36(1) and Article 38(1), if a marketing authorisation application is submitted in one or more Member States and in the United Kingdom in respect of Northern Ireland, or if a marketing authorisation application is submitted in the United Kingdom in respect of Northern Ireland for a medicinal product that is already being examined or has already been authorised in a Member State, the application regarding the United Kingdom in respect of Northern Ireland shall not have to be submitted in accordance with Chapter III, Sections 3 and 4, provided that all of the following conditions are fulfilled:

(a) the marketing authorisation for the United Kingdom in respect of Northern Ireland is granted by the competent authority for the United Kingdom in respect of Northern Ireland in compliance with Union law, and such compliance with Union law is ensured during the period of validity of that marketing authorisation;

(b) the medicinal products authorised by the competent authority for the United Kingdom in respect of Northern Ireland are made available to patients or end-consumers only in the territory of Northern Ireland, and they are not made available in any Member State.

3. Article 54(1), point (e), shall not apply to and in the United Kingdom in respect of Northern Ireland.

4. The holder of a marketing authorisation for a medicinal product for which a marketing authorisation has already been granted for the United Kingdom in respect of Northern Ireland in accordance with Chapter III, Sections 3 and 4, before 20 April 2022 shall be allowed to withdraw the marketing authorisation for the United Kingdom in respect of Northern Ireland from the mutual recognition procedure or the decentralised procedure and to submit an application for a marketing authorisation for that medicinal product to the competent authorities of the United Kingdom with respect to Northern Ireland in accordance with paragraph 2.

5. With regard to quality control testing referred to in Article 9 carried out in parts of the United Kingdom other than Northern Ireland regarding medicinal products included in the list referred to paragraph 10 of this Article other than those authorised by the Commission, the competent authorities of the United Kingdom in respect of Northern Ireland may consider that there is a justifiable case within the meaning of Article 9, point (b), without carrying out a case-by-case assessment provided that:

   (a) each batch of the medicinal products concerned is released by a qualified person on a site in the Union or in Northern Ireland or by a qualified person on a site in parts of the United Kingdom other than Northern Ireland applying quality standards that are equivalent to those laid down in Article 157;

(b) the establishment designated by the third party conducting the quality control testing is supervised by the competent authority of the United Kingdom, including by performing on-the-spot checks;

(c) where the batch release is carried out by a qualified person who resides and operates in parts of the United Kingdom other than Northern Ireland, the manufacturing authorisation holder declares that it does not have at its disposal a qualified person who resided and operated in the Union on 20 April 2022.

6. By way of derogation from Article 146(1), the competent authorities of the United Kingdom in respect of Northern Ireland shall allow medicinal products to be imported from parts of the United Kingdom other than Northern Ireland by wholesale distribution authorisation holders as referred to in Article 166(1) that are not in possession of a relevant manufacturing authorisation provided that all of the following conditions are fulfilled:

(a) the medicinal products have undergone quality control testing either in the Union, as provided for in Article 157(3), or in parts of the United Kingdom other than Northern Ireland in compliance with Article 9, point (b);

(b) the medicinal products have been subject to batch release by a qualified person in the Union in accordance with Article 157(1) or, for medicinal products authorised by the United Kingdom in respect of Northern Ireland, in parts of the United Kingdom other than Northern Ireland applying quality standards that are equivalent to those laid down in Article 157(1);

(c) the marketing authorisation for the medicinal product concerned has been granted in accordance with Union law, by the competent authority of a Member State or by the Commission or, as regards medicinal products placed on the market in Northern Ireland, by the competent authority of the United Kingdom in respect of Northern Ireland;

(d) medicinal products are only made available to patients or end-consumers in Northern Ireland;

7. For batches of medicinal products that are exported to parts of the United Kingdom other than Northern Ireland from a Member State and subsequently imported into Northern Ireland, the controls upon importation referred to in Article 157(1), first and second subparagraphs, shall not be required, provided that those batches have undergone such controls in a Member State prior to being exported to parts of the United Kingdom other than Northern Ireland and that they are accompanied by the control reports referred to in Article 157(1), third subparagraph.

8. Where the manufacturing authorisation is granted by the competent authority of the United Kingdom in respect of Northern Ireland, the qualified person referred to in Article 155 may reside and operate in parts of the United Kingdom other than Northern Ireland. This paragraph shall not apply where the manufacturing authorisation holder already has at its disposal a qualified person who resided and operated in the Union on 20 April 2022.

9. By way of derogation from the Article 102(5), where the marketing authorisation is granted by the competent authority of United Kingdom in respect of Northern Ireland, the qualified person referred to in Article 102(4), point (a), may reside and operate in parts of the United Kingdom other than Northern Ireland. This paragraph shall not apply where the marketing authorisation holder already has at its disposal a qualified person who resided and operated in the Union on 20 April 2022.

10. The competent authorities of the United Kingdom in respect of Northern Ireland shall publish on their website a list of medicinal products to which they have applied or intend to apply the derogations as set out in this Article and shall ensure that the list is updated at least on a six-monthly basis and managed in an independent manner.

Article 214

Regulatory functions carried out in the United Kingdom

1. The Commission shall continuously monitor developments in the United Kingdom that could affect the level of protection regarding the regulatory functions referred to in Article 102(4), Article 155(3), Article 213(6) and (7), that are carried out in parts of the United Kingdom other than Northern Ireland taking into account, in particular, the following elements:

   (a) the rules governing the granting of marketing authorisations, the obligations of the marketing authorisation holder, the granting of manufacturing authorisations, the obligations of the manufacturing authorisation holder, the qualified persons and their obligations, quality control testing, batch release and pharmacovigilance as laid down in United Kingdom law;

   (b) whether the competent authorities of the United Kingdom ensure the effective enforcement within their territory of the rules referred to in point (a), by means of, inter alia, inspections and audits of marketing authorisation holders, manufacturing authorisation holders and wholesale distributors located in their territories, and on-the-spot checks at their premises regarding the exercise of the regulatory functions referred to in point (a).

2. Where the Commission finds that the level of protection of public health ensured by the United Kingdom through rules governing the production, distribution and use of medicinal products as well as the effective enforcement of those rules is no longer essentially equivalent to that guaranteed within the Union, or where sufficient information is not available to the Commission to enable it to establish whether an essentially equivalent level of protection of public health is ensured by the United Kingdom, the Commission shall inform the United Kingdom through a written notification of that finding and of the detailed reasons therefor.

For a period of six months following the written notification made pursuant to the first subparagraph, the Commission shall enter into consultations with the United Kingdom with a view to remedying the situation giving rise to that written notification. In justified cases, the Commission may extend that period by three months.

3. If the situation giving rise to the written notification made pursuant to paragraph 2, first subparagraph, is not remedied within the time limit referred to in paragraph 2, second subparagraph, the Commission shall be empowered to adopt a delegated act amending or supplementing the provisions among those referred to in paragraph 1 whose application shall be suspended.

4. Where a delegated act pursuant to paragraph 3 has been adopted, the provisions referred to in the introductory sentence of paragraph 1 as specified in the delegated act shall cease to apply on the first day of the month following the entry into force of the delegated act.

5. Where the situation giving rise to the adoption of the delegated act pursuant to paragraph 3 has been remedied, the Commission shall adopt a delegated act specifying those suspended provisions that shall apply again. In that case, the provisions specified in the delegated act adopted pursuant to this paragraph shall apply again on the first day of the month following the entry into force of the delegated act adopted pursuant to this paragraph.

Article 215

Derogations for medicinal products placed on the market of Northern Ireland

The derogations set out in Article 213(2), (6), (7) and (8) shall not affect the obligations of the marketing authorisation holder to ensure the quality, safety and efficacy of the medicinal product placed on the market of Northern Ireland laid down in this Directive.

Chapter XVIII

Final provisions

Article 216

Amendment to the Annexes

The Commission is empowered to adopt delegated acts in accordance with Article 218 to amend Annexes I to VI in order to adapt them to scientific and technical progress and to amend Article 23 with regard to the ERA requirements set out in paragraphs 2, 3, 4 and 6 of that Article.

Article 217

Standing Committee on Medicinal Products for Human Use

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use. That Committee shall be a committee within the meaning of Regulation (EU) No 182/2011.

2. Where reference is made to this paragraph, Article 5 of Regulation (EU) No 182/2011 shall apply.

3. Where the opinion of the Standing Committee on Medicinal Products for Human Use is to be obtained by written procedure and reference is made to this paragraph, that procedure shall be terminated without result only when, within the time limit for delivery of the opinion, the chair of the Committee so decides.

4. The rules of procedure of the Standing Committee on Medicinal Products for Human Use shall be made publicly available.

5. The Standing Committee on Medicinal Products for Human Use shall ensure that its rules of procedure are adapted to the need to make medicinal products swiftly available to patients and take account of the tasks incumbent upon it under Chapter III and the procedure set out in Article 45.

Article 218

Exercise of the delegations

1. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.

2. The power to adopt delegated acts referred to in Article 5(2), Article 25(5), Article 26(9), Article 27(3) and (4), Article 31(2) and (3), Article 68(2), Article 70(2), Article 90, Article 94(4), Article 130(3), Article 154(3), Article 157(4), Article 163, Article 164, Article 193(1) and Article 216 shall be conferred on the Commission for a period of five years from … [date of entry into force of this Directive]. The Commission shall draw up a report in respect of the delegation of power not later than nine months before the end of the five-year period. The delegation of power shall be tacitly extended for periods of an identical duration, unless the European Parliament or the Council opposes such extension not later than three months before the end of each period.

   The power to adopt delegated acts referred to in Article 214(3) and (5) shall be conferred on the Commission for an indeterminate period of time from … [date of entry into force of this Directive].

3. The delegation of power referred to in Article 5(2), Article 25(5), Article 26(9), Article 27(3) and (4), Article 31(2) and (3), Article 68(2), Article 70(2), Article 90, Article 94(4), Article 130(3), Article 154(3), Article 157(4), Article 163, Article 164, Article 193(1), Article 214(3) and (5) and Article 216 may be revoked at any time by the European Parliament or by the Council. A decision to revoke shall put an end to the delegation of the power specified in that decision. It shall take effect the day following the publication of the decision in the *Official Journal of the European Union* or at a later date specified therein. It shall not affect the validity of any delegated acts already in force.

4. Before adopting a delegated act, the Commission shall consult experts designated by each Member State in accordance with the principles laid down in the Interinstitutional Agreement of 13 April 2016 on Better Law-Making.

5. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

6. A delegated act adopted pursuant to Article 5(2), Article 25(5), Article 26(9), Article 27(3) and (4), Article 31(2) and (3), Article 68(2), Article 70(2), Article 90, Article 94(4), Article 130(3), Article 154(3), Article 157(4), Article 163, Article 164, Article 193(1), Article 214(3) and (5) or Article 216 shall enter into force only if no objection has been expressed either by the European Parliament or by the Council within a period of two months of notification of that act to the European Parliament and the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by two months at the initiative of the European Parliament or of the Council.

Article 219

Report

1 By … [twelve years from the date of entry into force of this Directive], the Commission shall present a report to the European Parliament and the Council on the application of this Directive, including an assessment of the fulfilment of its objectives and the resources required to implement it. The report shall in particular include an assessment of:

(a) the revised framework for regulatory protection periods;

(b) the provisions to facilitate access to medicinal products laid down in Article 59;

(c) the appropriateness of the framework of homeopathic medicinal products;

(d) the application of adapted frameworks pursuant to Article 31.

The report shall be based, among other things, on information provided by Member States.

Where a Member State has applied Article 59, the information provided to the Commission shall include an assessment on whether the rules provided in that Article ensure timely availability and continuous supply of sufficient quantities of the medicinal product concerned in that Member State.

2. By … [twelve years from the date of entry into force of this Directive], the Commission shall present a report to the European Parliament and the Council on the application of Chapter VI. The report shall be based, among other things, on information provided by Member States and marketing authorisation holders It shall include an assessment on whether the level of digitalisation provided for in that Chapter remains appropriate. The Commission shall, if appropriate, present legislative proposals based on that assessment in order to amend this Directive or make further proposals, including on requiring the provision of the awareness card in electronic format only.

3. By … [seven years from the date of entry into force of this Directive], the Commission shall present a report to the European Parliament and the Council on the application of Article 23 and the impact of the ERA of medicinal products on the protection of human health and the environment. The report shall be based, among other things, on information provided by the Agency, the competent authorities of the Member States and the marketing authorisation holders. It shall include an assessment on whether the rules provided for in Article 23 appropriately contribute to risk mitigation for the environment and public health. When carrying out the assessment, the Commission shall take into account existing obligations in the field of environmental protection on economic operators already set out in Union law. The Commission shall, if appropriate, present legislative proposals based on that assessment in order to amend this Directive or make further proposals, including on expanding the scope of ERA to the manufacturing phase for all medicinal products.

Article 220

Repeals

1. Directive 2001/83/EC is repealed with effect from … [24 months from the date of entry into force of this Directive].

2. Directive 2009/35/EC is repealed with effect from … [24 months from the date of entry into force of this Directive].

3. References to the repealed Directives 2001/83/EC and 2009/35/EC shall be construed as references to this Directive. References to the repealed Directive 2001/83/EC shall be read in accordance with the correlation table in Annex VIII.

Article 221

Transitional provisions

1. The procedures concerning the marketing authorisation applications for medicinal products submitted in accordance with Article 19 of Directive 2001/83/EC before … [24 months from the date of entry into force of this Directive] and that are pending on … [the day before 24 months from the date of entry into force of this Directive] shall be completed in accordance with Directive 2001/83/EC.

2. Procedures initiated on the basis of Articles 29, 30, 31, and 107i of Directive 2001/83/EC before … [18 months from the date of entry into force of this Directive] and that are pending on … [the day before 24 months from the date of entry into force of this Directive] shall be completed in accordance with Articles 32 to 34 or Article 107k, as appropriate, of that Directive as applicable on … [the day before 24 months from the date of entry into force of this Directive].

3. This Directive shall also apply to medicinal products authorised in accordance with Directive 2001/83/EC before … [24 months from the date of entry into force of this Directive].

   This Directive shall also apply to registrations of homeopathic medicinal products and traditional herbal medicinal products carried out in accordance with Directive 2001/83/EC before … [24 months from the date of entry into force of this Directive].

4. By way of derogation from Chapter VI of this Directive, medicinal products placed on the market in accordance with Directive 2001/83/EC before … [24 months from the date of entry into force of this Directive] may continue to be made available on the market until … [seven years from the date of entry into force of this Directive], provided that they comply with the provisions on labelling and package leaflet set out in Title V of Directive 2001/83/EC as applicable on … [the day before 24 months from the date of entry into force of this Directive].

5. By way of derogation from Article 84 of this Directive, reference medicinal products for which the application for marketing authorisation has been submitted before … [24 months from the date of entry into force of this Directive] shall be subject to the provisions on data protection periods set out in Article 10 of Directive 2001/83/EC as applicable on … [24 months from the date of entry into force of this Directive].

6. By way of derogation from paragraph 3 of this Article, the reporting obligations as referred to in Article 60 of this Directive, shall not apply with regards to medicinal products authorised in accordance with Directive 2001/83/EC before … [24 months from the date of entry into force of this Directive].

7. For medicinal products authorised before … [24 months from the date of entry into force of this Directive] and for which the validity of the marketing authorisation expires after that date, the renewal of the marketing authorisation shall follow the procedures referred to in Article 49.

8. Medicinal products placed on the market prior to … [24 months from the date of entry into force of this Directive] which do not comply with the requirements of this Directive may be marketed until the stocks of the medicinal products are exhausted.

9. The requirement to make the package leaflet available electronically, pursuant to Article 66(1) shall apply as follows:

(a) for medicinal products for which the application for marketing authorisation was submitted after … [24 months from the date of entry into force of this Directive], it shall apply immediately, provided that the implementing acts referred to in Article 66(6) are adopted;

(b) for medicinal products authorised before … [date of entry into force of this Directive] and medicinal products for which the marketing authorisation application was submitted before … [24 months from the date of entry into force of this Directive], it shall apply on … [five years from the date of entry into force of this Directive], unless a marketing authorisation holder chooses to comply with the requirement earlier and provided that the implementing acts referred to in Article 66(6) are adopted.

10. Medicinal products authorised before … [date of entry into force of this Directive] which do not comply with the requirement to make the package leaflet available electronically, pursuant to Article 66(1) may continue to be placed on the market, distributed, dispensed, sold and used until stocks of those medicinal products are exhausted.

11. The competent authorities of Malta may maintain in force marketing authorisations that were granted, extended or maintained in accordance with Article 126c of Directive 2001/83/EC and that are valid at the time of entry into force of this Directive, until … [five years and six months from the date of entry into force of this Directive].

Article 222

Transposition

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by … [24 months from the date of entry into force of this Directive]. They shall immediately communicate the text of those measures to the Commission. Member States shall apply those measures from … [24 months from the date of entry into force of this Directive].

2. However, Member States may apply Article 59 of this Directive as from … [12 months from the date of entry into force of this Directive] in respect of medicinal products authorised after the date of entry into force of this Directive. In the case of a medicinal product which has been granted a marketing authorisation in accordance with Regulation (EC) No 726/2004 or Directive 2001/83/EC between …[date of entry into force of this Directive] and … [24 months from the date of entry into force of this Directive], Article 10(1), second subparagraph, of Directive 2001/83/EC shall not apply in the Member State that made a request in accordance with Article 59 of this Directive, if the marketing authorisation holder has not made the medicinal product available and has not supplied it continuously in that Member State in accordance with Article 59 of this Directive.

3. When Member States adopt those measures, they shall contain a reference to this Directive or shall be accompanied by such reference on the occasion of their official publication. They shall also include a statement that references in existing laws, regulations and administrative provisions to the Directives repealed by this Directive shall be construed as references to this Directive. Member States shall determine how such reference is to be made and how that statement is to be formulated.

4. Member States shall communicate to the Commission the text of the main measures of national law that they adopt in the field covered by this Directive.

Article 223

Entry into force

This Directive shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

Article 224

Addressees

This Directive is addressed to the Member States.

Done at Strasbourg, …

For the European Parliament	*For the Council*
The President	*The President*

ANNEX I

Information to be included in the marketing authorisation application

(1) Name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.

(2) Name of the medicinal product.

(3) Qualitative and quantitative particulars of all the constituents of the medicinal product, including the reference to its international non-proprietary name (INN) recommended by the World Health Organization, where an INN for the medicinal product exists, or a reference to the relevant chemical name.

(4) An environmental risk assessment (ERA) in accordance with the requirements laid down in Articles 23 and 24.

(5) For medicinal products consisting of or containing genetically modified organisms, an ERA identifying and characterising possible hazards for human health, animals and the environment. The ERA shall be conducted in accordance with the elements described in Article 8 of Regulation (EU) 2026/…[+] and the requirements of Annex II to this Directive, based on the principles set out in Annex II to Directive 2001/18/EC of the European Parliament and of the Council[1] taking into account the specificities of medicinal products.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

[1] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJ L 106, 17.4.2001, p. 1, ELI: http://data.europa.eu/eli/dir/2001/18/oj).

(6) Description of the manufacturing method.

(7) Therapeutic indications, contra-indications and adverse reactions.

(8) Posology, pharmaceutical form, method and route of administration and expected shelf life.

(9) Reasons for any precautionary and safety measures to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of potential risks presented by the medicinal product for the environment.

(10) Description of the control methods employed by the manufacturer.

(11) A written confirmation that the manufacturer of the medicinal product has verified compliance by the manufacturer of the active substance with the principles of good manufacturing practice referred to in Article 163 by conducting audits, in accordance with Article 151. The written confirmation shall contain a reference to the date of the audit and a declaration that the outcome of the audit confirms that the manufacturing complies with the principles of good manufacturing practice.

(12) Results of:

(a) pharmaceutical (physico-chemical, biological or microbiological) tests,

(b) non-clinical (toxicological and pharmacological) tests,

(c) clinical trials.

(13) Where relevant, evidence from other sources of clinical data (non-interventional clinical studies, registries).

(14) A summary of the applicant's pharmacovigilance system including the following elements:

(a) proof that the applicant has at its disposal a qualified person responsible for pharmacovigilance,

(b) the Member States in which the qualified person resides and carries out its tasks,

(c) the contact details of the qualified person,

(d) a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Chapter IX,

(e) a reference to the location where the pharmacovigilance system master file for the medicinal product is kept.

(15) The risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned, together with a summary thereof.

(16) A statement to the effect that clinical trials carried out outside the Union meet the ethical requirements of Regulation (EU) No 536/2014.

(17) A summary of product characteristics in accordance with Article 65, a mock-up of the outer packaging, containing the details provided for in Annex IV and of the immediate packaging of the medicinal product, containing the details provided for in Article 69, together with a package leaflet in accordance with Article 67.

(18) A document showing that the manufacturer is authorised in its own country to produce medicinal products.

(19) Copies of the following:

(a) any marketing authorisation, whether obtained in another Member State or in a third country, to place the medicinal product on the market, a summary of the safety data including the data contained in the periodic safety update reports, where available, and suspected adverse reactions reports, together with a list of those Member States in which an application for a marketing authorisation submitted in accordance with this Directive is under examination;

(b) the summary of product characteristics proposed by the applicant in accordance with Article 65 or approved by the competent authorities of the Member State in accordance with Article 46 and the package leaflet proposed in accordance with Article 67 or approved by the competent authorities of the Member State in accordance with Article 79;

(c) details of any decision to refuse a marketing authorisation, whether in the Union or in a third country, and the reasons for such a decision.

(20) A copy of the Agency's decision granting the orphan designation referred to in Article 66 of Regulation (EU) 2026/…[+], accompanied by a copy of the Agency's relevant scientific conclusions justifying its decision.

(21) Where the marketing authorisation application concerns an antimicrobial, it shall also contain:

(a) an antimicrobial stewardship plan including in particular:

(i) information about risk mitigation measures to limit antimicrobial resistance development related to the use, prescription and administration of the medicinal product;

(ii) information on how the marketing authorisation holder intends to monitor and report to the competent authority of the Member State or the Agency, as applicable, the resistance to the antimicrobial;

(iii) information about measures to monitor effectiveness of stewardship;

(b) a description of the special information requirements outlined in Article 72

(c) details on the pack size corresponding to the usual posology and duration of treatment.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

(22) The marketing authorisation application for a radionuclide generator shall, in addition to the requirements set out in Articles 7 and 10, contain:

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Introduction and general principles

(1) The particulars and documents accompanying an application for marketing authorisation pursuant to Article 8 and Article 10(1) shall be presented in accordance with the requirements set out in this Annex and shall follow the guidance published by the Commission in 'The rules governing medicinal products in the European Community', Volume 2 B, Notice to applicants, Medicinal products for human use, Presentation and content of the dossier, Common Technical Document (CTD) ('European Community-CTD-presentation').

(2) The particulars and documents shall be presented as five modules: Module 1 provides the European Union specific administrative data; Module 2 provides quality, non-clinical and clinical summaries, Module 3 provides chemical, pharmaceutical and biological information, Module 4 provides non-clinical reports and Module 5 provides clinical study reports. This presentation implements a common format for all ICH[1] regions (European Union, United States of America, Japan). These five Modules shall be presented in strict accordance with the format, content and numbering system delineated in details in Volume 2 B of the Notice to Applicants referred to in point (1).

[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

(3) The European Community-CTD-presentation is applicable for all types of marketing authorisation applications irrespective of the procedure to be applied (i.e. centralised, mutual recognition or national) and of whether they are based on a full, abridged, bibliographic or consent-based application. It is also applicable for all types of products including new chemical entities (NCE), radio-pharmaceuticals, plasma derivatives, vaccines, herbal medicinal products, etc.

(4) In assembling the dossier for application for marketing authorisation, applicants shall also take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use as adopted by the Committee for Proprietary Medicinal Products / Committee for Medicinal Products for Human Use and published by the European Medicine Evaluation Agency / the Agency and the other pharmaceutical Union guidelines published by the Commission in the different volumes of 'The rules governing medicinal products in the European Community'.

(5) With respect to the quality part (chemical, pharmaceutical and biological) of the dossier, all monographs including general monographs and general chapters of the European Pharmacopoeia are applicable.

(6) The manufacturing process shall comply with the requirements of Directive (EU) 2017/1572 and with the principles and guidelines on GMP, published by the Commission in 'The rules governing medicinal products in the European Community', Volume 4.

(7) All information which is relevant to the evaluation of the medicinal product concerned shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned pharmaco-toxicological or clinical test or trial relating to the medicinal product and/or completed trials concerning therapeutic indications not covered by the application.

(8) All clinical trials conducted within the Union, must comply with the requirements of Regulation (EU) No 536/2014. To be taken into account during the assessment of an application, clinical trials conducted outside the Union, which relate to medicinal products intended to be used in the Union, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Regulation (EU) No 536/2014. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki.

(9) Non-clinical (pharmaco-toxicological) studies shall be carried out in conformity with the provisions related to Good Laboratory Practice laid down in Directives 2004/9/EC[2] and 2004/10/EC[3] of the European Parliament and of the Council.

(10) Member States shall also ensure that all tests on animals are conducted in accordance with Directive 2010/63/EU.

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[2] Directive 2004/9/EC of the European Parliament and of the Council of 11 February 2004 on the inspection and verification of good laboratory practice (GLP) (OJ L 50, 20.2.2004, p. 28, ELI: http://data.europa.eu/eli/dir/2004/9/oj).

[3] Directive 2004/10/EC of the European Parliament and of the Council of 11 February 2004 on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances (OJ L 50, 20.2.2004, p. 44, ELI: http://data.europa.eu/eli/dir/1987/18/oj).

(11) In order to monitor the benefit/risk assessment, any new information not in the original application and all pharmaco-vigilance information shall be submitted to the competent authority. After marketing authorisation has been granted, any change to the data in the dossier shall be submitted to the competent authorities in accordance with the requirements of Commission Regulation (EC) No 1234/2008[4] or, if relevant, in accordance with national provisions, as well as the requirements in the Commission publication 'The rules governing medicinal products in the European Community', Volume 9.

This Annex is divided in four different parts:

– Part I describes the application format, the summary of product characteristics, the labelling, the package leaflet and presentation requirements for standard applications (Modules 1 to 5).

– Part II provides derogation for 'Specific applications', i.e. well-established medicinal use, essentially similar products, fixed-dose combinations, similar biological products, exceptional circumstances and mixed applications (part bibliographic and part own studies).

– Part III deals with 'Particular application requirements' for biological medicinal products (Plasma Master File; Vaccine Antigen Master File), radio-pharmaceuticals, homeopathic medicinal products, herbal medicinal products and orphan medicinal products.

[4] Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7, ELI: http://data.europa.eu/eli/reg/2008/1234/oj).

– Part IV deals with ‘Advanced therapy medicinal products’ and concerns specific requirements for gene therapy medicinal products (using human autologous or allogeneic system, or xenogeneic system) and cell therapy medicinal products both of human or animal origin and xenogeneic transplantation medicinal products.

PART I

STANDARDISED MARKETING AUTHORISATION DOSSIER REQUIREMENTS

1. MODULE 1: ADMINISTRATIVE INFORMATION

1.1. **Table of contents**

A comprehensive table of contents of Modules 1 to 5 of the dossier submitted for marketing authorisation application shall be presented.

1.2. **Application form**

The medicinal product, which is the subject of the application, shall be identified by name and name of the active substance(s), together with the pharmaceutical form, the route of administration, the strength and the final presentation, including packaging.

The name and address of the applicant shall be given, together with the name and address of the manufacturers and the sites involved in the different stages of the manufacture (including the manufacturer of the finished product and the manufacturer(s) of the active substance(s)), and where relevant the name and address of the importer.

The applicant shall identify the type of application and indicate what samples, if any, are also provided.

Annexed to the administrative data shall be copies of the manufacturing authorisation as defined in Article 146, together with a list of countries in which authorisation has been granted, copies of all the summaries of product characteristics in accordance with Article 65 as approved by Member States and a list of countries in which an application has been submitted.

As outlined in the application form, the applicants shall provide, inter alia, details of the medicinal product subject of the application, the legal basis of the application, the proposed marketing authorisation holder and manufacture(s), information on orphan medicinal product status, scientific advice and paediatric development program.

1.3. **Summary of product characteristics, labelling and package leaflet**

1.3.1 *Summary of product characteristics*

The applicant shall propose a summary of the product characteristics, in accordance with Article 65.

1.3.2. *Labelling and package leaflet*

A proposed labelling text for immediate and outer packaging as well as for the package leaflet shall be provided. These shall be in accordance with all mandatory items listed in Articles 66 to 82 on the labelling of medicinal products for human use and on package leaflet, and in Annexes IV and VI.

1.3.3. *Mock-ups and specimens*

The applicant shall provide specimen and/or mock-ups of the immediate and outer packaging, labels and package leaflets for the medicinal product concerned.

1.3.4. *Summaries of product characteristics already approved in the Member States*

Annexed to the administrative data of the application form shall be copies of all the summaries of product characteristics in accordance with Article 65 and Article 46(1) to (5) as approved by Member States, where applicable, and a list of countries in which an application has been submitted.

1.4. **Information about the experts**

In accordance with Article 8(2) experts must provide detailed reports of their observations on the documents and particulars which constitute the marketing authorisation dossier and in particular on Modules 3, 4 and 5 (chemical, pharmaceutical and biological documentation, non-clinical documentation and clinical documentation, respectively). The experts are required to address the critical points related to the quality of the medicinal product and of the investigations carried out on animals and human beings and bring out all the data relevant for evaluation.

These requirements shall be met by providing a quality overall summary, a non-clinical overview (data from studies carried out in animals) and a clinical overview that shall be located in Module 2 of the marketing authorisation application dossier. A declaration signed by the experts together with brief information on their educational background, training and occupational experience shall be presented in Module 1. The experts shall have suitable technical or professional qualifications. The professional relationship of the expert to the applicant shall be declared.

1.5. **Specific requirements for different types of applications**

Specific requirements for different types of applications are addressed in Part II of this Annex.

1.6. **Environmental risk assessment**

Where applicable, applications for marketing authorisations shall include a risk assessment overview evaluating possible risks to the environment due to the use and/or disposal of the medicinal product and make proposals for appropriate labelling provisions. Environmental risk connected with the release of medicinal products consisting of or containing genetically modified organisms (GMOs) within the meaning of Article 2 of Directive 2001/18/EC shall be addressed.

Information pertaining to the environmental risk shall appear as an appendix to Module 1.

The information shall be presented in accordance with the provisions of Directive 2001/18/EC, taking into account any guidance documents published by the Commission in connection with the implementation of that Directive.

The information shall consist of:

– an introduction;

– a copy of any written consent or consents to the deliberate release into the environment of the GMO(s) for research and development purposes according to Part B of Directive 2001/18/EC;

– the information requested in Annexes II to IV of Directive 2001/18/EC, including detection and identification methods as well as the unique identifier of the GMO, plus any additional information on the GMO or the product of relevance for evaluating the environmental risk;

– an environment risk assessment (ERA) report prepared on the basis of the information specified in Annexes III and IV of Directive 2001/18/EC and in accordance with Annex II of that Directive;

– taking into account the above information and the ERA, a conclusion which proposes an appropriate risk management strategy which includes, as relevant to the GMO and product in question, a post-market monitoring plan and the identification of any special particulars which need to appear in the summary of product characteristics, labelling and package leaflet;

– appropriate measures in order to inform the public.

A dated signature of the author, information on the author's educational, training and occupational experience, and a statement of the author's relationship with the applicant, shall be included.

2. MODULE 2: SUMMARIES

This Module aims to summarise the chemical, pharmaceutical and biological data, the non-clinical data and the clinical data presented in Modules 3, 4 and 5 of the dossier for marketing authorisation, and to provide the reports/overviews described in Article 8 of this Directive.

Critical points shall be addressed and analysed. Factual summaries including tabular formats shall be provided. Those reports shall provide cross-references to tabular formats or to the information contained in the main documentation presented in Module 3 (chemical, pharmaceutical and biological documentation), Module 4 (non-clinical documentation) and Module 5 (clinical documentation).

The information contained in Module 2 shall be presented in accordance with the format, content and numbering system delineated in the Volume 2 of the Notice to Applicants. The overviews and summaries shall comply with the basic principles and requirements as laid down herewith:

2.1. **Overall table of contents**

Module 2 shall contain a table of contents for the scientific documentation submitted in Modules 2 to 5.

2.2. **Introduction**

Information on the pharmacological class, mode of action and proposed clinical use of the medicinal product for which a marketing authorisation is requested shall be supplied.

2.3. **Quality overall summary**

A review of the information related to the chemical, pharmaceutical and biological data shall be provided in a quality overall summary.

Key critical parameters and issues related to quality aspects shall be emphasised as well as justification in cases where the relevant guidelines are not followed. This document shall follow the scope and outline of the corresponding detailed data presented in Module 3.

2.4. **Non-clinical overview**

An integrated and critical assessment of the non-clinical evaluation of the medicinal product in animals/*in vitro* shall be required. Discussion and justification of the testing strategy and of deviation from the relevant guidelines shall be included.

Except for biological medicinal products, an assessment of the impurities and degradation products shall be included along with their potential pharmacological and toxicological effects. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the non-clinical studies and the product to be marketed shall be discussed.

For biological medicinal products, comparability of material used in non-clinical studies, clinical studies, and the medicinal product for marketing shall be assessed.

Any novel excipient shall be the subject of a specific safety assessment.

The characteristics of the medicinal product, as demonstrated by the non-clinical studies shall be defined and the implications of the findings for the safety of the medicinal product for the intended clinical use in human shall be discussed.

2.5. **Clinical overview**

The clinical overview is intended to provide a critical analysis of the clinical data included in the clinical summary and Module 5. The approach to the clinical development of the medicinal product, including critical study design, decisions related to and performance of the studies shall be provided.

A brief overview of the clinical findings, including important limitations as well as an evaluation of benefits and risks based on the conclusions of the clinical studies shall be provided. An interpretation of the way the efficacy and safety findings support the proposed dose and target indications and an evaluation of how the summary of product characteristics and other approaches will optimise the benefits and manage the risks is required.

Efficacy or safety issues encountered in development, and unresolved issues, shall be explained.

2.6. **Non-clinical summary**

The results of pharmacology, pharmaco-kinetics and toxicology studies carried out in animals/*in vitro* shall be provided as factual written and tabulated summaries which shall be presented in the following order:

– Introduction

– Pharmacology Written Summary

– Pharmacology Tabulated Summary

– Pharmaco-kinetics Written Summary

– Pharmaco-kinetics Tabulated Summary

– Toxicology Written Summary

– Toxicology Tabulated Summary.

2.7. **Clinical Summary**

A detailed, factual summary of the clinical information on the medicinal product included in Module 5 shall be provided. This shall include the results of all bio-pharmaceutics studies, of clinical pharmacology studies, and of clinical efficacy and safety studies. A synopsis of the individual studies is required.

Summarised clinical information shall be presented in the following order:

– Summary of Bio-pharmaceutics and Associated Analytical Methods

– Summary of Clinical Pharmacology Studies

– Summary of Clinical Efficacy

– Summary of Clinical Safety

– Synopses of Individual Studies

3. MODULE 3: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL INFORMATION FOR MEDICINAL PRODUCTS CONTAINING CHEMICAL AND/OR BIOLOGICAL ACTIVE SUBSTANCES

3.1. **Format and presentation**

The general outline of Module 3 is as follows:

– Table of contents

– Body of data

– *Active substance*

General Information

– Nomenclature

– Structure

– General Properties

Manufacture

– Manufacturer(s)

– Description of Manufacturing Process and Process Controls

– Control of Materials

– Controls of Critical Steps and Intermediates

– Process Validation and/or Evaluation

– Manufacturing Process Development

Characterisation

– Elucidation of Structure and other Characteristics

– Impurities

Control of Active Substance

– Specification

– Analytical Procedures

– Validation of Analytical Procedures

– Batch Analyses

– Justification of Specification

Reference Standards or Materials

Container Closure System

Stability

– Stability Summary and Conclusions

– Post-approval Stability Protocol and Stability Commitment

– Stability Data

– *Finished Medicinal Product*

Description and Composition of the Medicinal Product

Pharmaceutical Development

– Components of the Medicinal Product

  – Active Substance

  – Excipients

– Medicinal Product

  – Formulation Development

  – Overages

  – Physicochemical and Biological Properties

  – Manufacturing Process Development

– Container Closure System

– Microbiological Attributes

– Compatibility

Manufacture

– Manufacturer(s)

– Batch Formula

– Description of Manufacturing Process and Process Controls

– Controls of Critical Steps and Intermediates

– Process Validation and/or Evaluation

Control of Excipients

– Specifications

– Analytical Procedures

– Validation of Analytical Procedures

– Justification of Specifications

– Excipients of Human or Animal Origin

– Novel Excipients

Control of Finished Medicinal Product

- Specification(s)
- Analytical Procedures
- Validation of Analytical Procedures
- Batch Analyses
- Characterisation of Impurities
- Justification of Specification(s)

Reference Standards or Materials

Container Closure System

Stability

- Stability Summary and Conclusion
- Post-approval Stability Protocol and Stability Commitment
- Stability Data

– *Appendices*

- Facilities and Equipment (Biological Medicinal Products only)

- Adventitious Agents Safety Evaluation
- Excipients

- *Union Additional Information*
  - Process Validation Scheme for the Medicinal Product
  - Medical Device
  - Certificate(s) of Suitability
  - Medicinal products containing or using in the manufacturing process materials of animal and/or human origin (TSE procedure)

- Literature References

3.2. **Content: basic principles and requirements**

(1) The chemical, pharmaceutical and biological data that shall be provided shall include for the active substance(s) and for the finished medicinal product all of relevant information on: the development, the manufacturing process, the characterisation and properties, the quality control operations and requirements, the stability as well as a description of the composition and presentation of the finished medicinal product.

(2) Two main sets of information shall be provided, dealing with the active substance(s) and with the finished medicinal product, respectively.

(3) This Module shall in addition supply detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the finished medicinal product.

(4) All the procedures and methods used for manufacturing and controlling the active substance and the finished medicinal product shall be described in sufficient details to enable them to be repeated in control tests, carried out at the request of the competent authority. All test procedures shall correspond to the state of scientific progress at the time and shall be validated. Results of the validation studies shall be provided. In the case of test procedures included in the European Pharmacopoeia, this description shall be replaced by the appropriate detailed reference to the monograph(s) and general chapter(s) of the European Pharmacopoeia.

(5) The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia.

However, where a material in the European Pharmacopoeia or in the pharmacopoeia of a Member State has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits shall be declared and a suitable test procedure shall be described. In cases where a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorisation holder. The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorisation holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.

In the case of analytical procedures included in the European Pharmacopoeia, this description shall be replaced in each relevant section by the appropriate detailed reference to the monograph(s) and general chapter(s) of the European Pharmacopoeia.

(6) In the case where the starting and raw materials, active substance(s) or excipient(s) are described neither in the European Pharmacopoeia nor in the pharmacopoeia of a Member State, compliance with the monograph of a third country pharmacopoeia can be accepted. In such cases, the applicant shall submit a copy of the monograph accompanied by the validation of the analytical procedures contained in the monograph and by a translation where appropriate.

(7) Where the active substance and/or a raw and starting material or excipient(s) are the subject of a monograph of the European Pharmacopoeia, the applicant can apply for a certificate of suitability that, where granted by the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe, shall be presented in the relevant section of this Module. Those certificates of suitability of the monograph of the European Pharmacopoeia are deemed to replace the relevant data of the corresponding sections described in this Module. The manufacturer shall give the assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability by the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe.

(8) For a well-defined active substance, the active substance manufacturer or the applicant may arrange for the

(i) detailed description of the manufacturing process,

(ii) quality control during manufacture, and

(iii) process validation

to be supplied in a separate document directly to the competent authorities by the manufacturer of the active substance as an Active Substance Master File.

In this case, the manufacturer shall, however, provide the applicant with all of the data, which may be necessary for the latter to take responsibility for the medicinal product. The manufacturer shall confirm in writing to the applicant that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing the applicant. Documents and particulars supporting the application for such a change shall be supplied to the competent authorities; these documents and particulars will be also supplied to the applicant when they concern the open part of the active substance master file.

(9) Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies (materials from ruminant origin): at each step of the manufacturing process, the applicant shall demonstrate the compliance of the materials used with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the *Official Journal of the European Union*. Demonstration of compliance with the said Note for Guidance can be done by submitting either, preferably a certificate of suitability to the relevant monograph of the European Pharmacopoeia that has been granted by the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe or by the supply of scientific data to substantiate this compliance.

(10) For adventitious agents, information assessing the risk with respect to potential contamination with adventitious agents, whether they are non-viral or viral, as laid down in relevant guidelines as well as in relevant general monograph and general chapter of the European Pharmacopoeia, shall be provided.

(11) Any special apparatus and equipment, which may be used at any stage of the manufacturing process and control operations of the medicinal product, shall be described in adequate details.

(12) Where, in accordance with Article 1(8), second subparagraph, or Article 1(9), second subparagraph, of Regulation (EU) 2017/745, a product is governed by this Directive, the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device.

If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) 2017/745, the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation issued by a notified body designated in accordance with that Regulation for the type of device in question.

3.2.1 *Active substance(s)*

3.2.1.1. General information and information related to the starting and raw materials

a) Information on the nomenclature of the active substance shall be provided, including the recommended International Non-proprietary Name (INN), European Pharmacopoeia name if relevant, and chemical name(s).

The structural formula, including relative and absolute stereo-chemistry, the molecular formula and the relative molecular mass, shall be provided. For biotechnological medicinal products if appropriate, the schematic amino acid sequence and relative molecular mass shall be provided.

A list shall be provided of physicochemical and other relevant properties of the active substance, including biological activity for biological medicinal products.

b) For the purposes of this Annex, ‘starting materials’, as regards biological medicinal products, means any substance of biological origin such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells).

The following shall be considered as biological medicinal products: immunological medicinal products and medicinal products derived from human blood and human plasma; medicinal products falling within the scope of Annex I to Regulation (EU) No 2026/…[+]; advanced therapy medicinal products as defined in Article 5(1), point (8), of this Directive.

Any other substances used for manufacturing or extracting the active substance(s) but from which this active substance is not directly derived, such as reagents, culture media, foetal calf serum, additives, and buffers involved in chromatography, etc. are known as raw materials.

3.2.1.2. Manufacturing process of the active substance(s)

a) The description of the active substance manufacturing process represents the applicant's commitment for the manufacture of the active substance. To adequately describe the manufacturing process and process controls, appropriate information as laid down in guidelines published by the Agency shall be provided.

b) All materials needed in order to manufacture the active substance(s) shall be listed, identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.

Raw materials shall be listed and their quality and controls shall also be documented.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD).

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.

c) For biological medicinal products, the following additional requirements shall apply.

The origin and history of the starting materials shall be described and documented.

Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant shall demonstrate that the active substance complies with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the *Official Journal of the European Union*.

When cell banks are used, the cell characteristics shall be shown to have remained unchanged at the passage level used for production and beyond.

Seed materials, cell banks, pools of serum or plasma and other materials of biological origin and, whenever possible, the materials from which they are derived shall be tested for adventitious agents.

If the presence of potentially pathogenic adventitious agents is inevitable, the corresponding material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.

Whenever possible, vaccine production shall be based on a seed lot system and on established cell banks. For bacterial and viral vaccines, the characteristics of the infectious agent shall be demonstrated on the seed. In addition, for live vaccines, the stability of the attenuation characteristics shall be demonstrated on the seed; if this proof is not sufficient, the attenuation characteristics shall also be demonstrated at the production stage.

For medicinal products derived from human blood or plasma, the origin and the criteria and procedures for collection, transportation and storage of the starting material shall be described and documented in accordance with provisions laid down in Part III of this Annex.

The manufacturing facilities and equipment shall be described.

d) Tests and acceptance criteria carried out at every critical step, information on the quality and control of intermediates and process validation and/or evaluation studies shall be provided as appropriate.

e) If the presence of potentially pathogenic adventitious agents is inevitable, the correspondent material shall be used only when further processing ensures their elimination and/or inactivation and this shall be validated in the section dealing with viral safety evaluation.

f) A description and discussion of the significant changes made to the manufacturing process during development and/or manufacturing site of the active substance shall be provided.

3.2.1.3. Characterisation of the active substance(s)

Data highlighting the structure and other characteristics of the active substance(s) shall be provided.

Confirmation of the structure of the active substance(s) based on any physico-chemical and/or immuno-chemical and/or biological methods, as well as information on impurities shall be provided.

3.2.1.4. Control of active substance(s)

Detailed information on the specifications used for routine control of active substance(s), justification for the choice of these specifications, methods of analysis and their validation shall be provided.

The results of control carried out on individual batches manufactured during development shall be presented.

3.2.1.5. Reference standards or materials

Reference preparations and standards shall be identified and described in detail. Where relevant, chemical and biological reference material of the European Pharmacopoeia shall be used.

3.2.1.6. Container and closure system of the active substance

A description of the container and the closure system(s) and their specifications shall be provided.

3.2.1.7. Stability of the active substance(s)

a) The types of studies conducted, protocols used, and the results of the studies shall be summarised

b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format

c) The post-authorisation stability protocol and stability commitment shall be provided

3.2.2 *Finished medicinal product*

3.2.2.1 Description and composition of the finished medicinal product

A description of the finished medicinal product and its composition shall be provided. The information shall include the description of the pharmaceutical form and composition with all the constituents of the finished medicinal product, their amount on a per-unit basis, the function of the constituents of:

– the active substance(s),

– the constituent(s) of the excipients, whatever their nature or the quantity used, including colouring matter, preservatives, adjuvants, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, etc.,

– the constituents, intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products (hard capsules, soft capsules, rectal capsules, coated tablets, films-coated tablets, etc.),

– these particulars shall be supplemented by any relevant data concerning the type of container and, where appropriate, its manner of closure, together with details of devices with which the medicinal product will be used or administered and which will be delivered with the medicinal product.

The 'usual terminology', to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions in point (3) of Annex I:

– in respect of substances which appear in the European Pharmacopoeia or, failing this, in the national pharmacopoeia of one of the Member States, the main title at the head of the monograph in question, with reference to the pharmacopoeia concerned,

– in respect of other substances, the international non-proprietary name (INN) recommended by the World Health Organisation, or, failing this, the exact scientific designation; substances not having an international non-proprietary name or an exact scientific designation shall be described by a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details,

– in respect of colouring matter, designation as laid down in the implementing acts adopted pursuant to Article 30(3) of this Directive and/or in Regulation (EC) No 1333/2008 of the European Parliament and of the Council[5].

[5] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives (OJ L 354, 31.12.2008, p. 16, ELI: http://data.europa.eu/eli/reg/2008/1333/oj).

In order to give the ‘quantitative composition’ of the active substance(s) of the finished medicinal products, it is necessary, depending on the pharmaceutical form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance.

Active substances present in the form of compounds or derivatives shall be designated quantitatively by their total mass, and if necessary or relevant, by the mass of active entity or entities of the molecule.

For medicinal products containing an active substance, which is the subject of an application for marketing authorisation in any Member State for the first time, the quantitative statement of an active substance, which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently authorised medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active substance.

Units of biological activity shall be used for substances, which cannot be defined molecularly. Where an International Unit of biological activity has been defined by the World Health Organisation, this shall be used. Where no International Unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances by using where applicable the European Pharmacopoeia Units.

3.2.2.2. Pharmaceutical development

This section shall be devoted to information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the intended use specified in the marketing authorisation application dossier.

The studies described in this section are distinct from routine control tests conducted according to specifications. Critical parameters of the formulation and process attributes that can influence batch reproducibility, medicinal product performance and medicinal product quality shall be identified and described. Additional supportive data, where appropriate, shall be referenced to the relevant sections of Module 4 (Non Clinical Study Reports) and Module 5 (Clinical Study Reports) of the marketing authorisation application dossier.

a) The compatibility of the active substance with excipients as well as key physicochemical characteristics of the active substance that can influence the performance of the finished product or the compatibility of different active substances with each other in the case of combination products, shall be documented.

b) The choice of excipients, in particular relative to their respective functions and concentration shall be documented.

c) A description of the development of the finished product shall be provided, taking into consideration the proposed route of administration and usage.

d) Any overages in the formulation(s) shall be warranted.

e) As far as the physiochemical and biological properties are concerned, any parameter relevant to the performance of finished product shall be addressed and documented.

f) The selection and optimisation of the manufacturing process as well as differences between the manufacturing process(es) used to produce pivotal clinical batches and the process used for manufacturing the proposed finished medicinal product shall be provided.

g) The suitability of the container and closure system used for the storage, shipping and use of the finished product shall be documented. A possible interaction between medicinal product and container may need to be considered.

h) The microbiological attributes of the dosage form in relation with non-sterile and sterile products shall be in accordance with and documented as prescribed in the European Pharmacopoeia.

i) In order to provide appropriate and supportive information for the labelling the compatibility of the finished product with reconstitution diluent(s) or dosage devices shall be documented

3.2.2.3. Manufacturing process of the finished medicinal product

a) The description of the manufacturing method accompanying the application for Marketing Authorisation pursuant to point (6) of Annex I shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.

For this purpose it shall include at least:

– mention of the various stages of manufacture including process controls and corresponding acceptance criteria, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents,

– in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished product,

– experimental studies validating the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the product,

– for sterile medicinal products, details of the sterilisation processes and/or aseptic procedures used,

– a detailed batch formula.

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.

b) Particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the production process shall be included.

These tests are essential for checking the conformity of the medicinal product with the formula when, exceptionally, an applicant proposes an analytical method for testing the finished product which does not include the assay of all the active substances (or of all the excipient constituents subject to the same requirements as the active substances).

The same applies where the quality control of the finished product depends on in-process control tests, particularly if the medicinal product is essentially defined by its method of preparation.

c) Description, documentation, and results of the validation studies for critical steps or critical assays used in the manufacturing process shall be provided.

3.2.2.4. Control of excipients

a) All the materials needed in order to manufacture the excipient(s) shall be listed identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.

Colouring matter shall, in all cases, satisfy the requirements of this Directive and/or Regulation (EC) No 1333/2008. In addition, colouring matter shall meet purity criteria as laid down in Commission Regulation (EU) No 231/2012[6].

[6] Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council (OJ L 83, 22.3.2012, p. 1, ELI: http://data.europa.eu/eli/reg/2012/231/oj).

b) For each excipient, the specifications and their justifications shall be detailed. The analytical procedures shall be described and duly validated.

c) Specific attention shall be paid to excipients of human or animal origin.

Regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate also for excipients that the medicinal product is manufactured in accordance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published by the Commission in the *Official Journal of the European Union*.

Demonstration of compliance with the aforementioned Note for Guidance can be done by submitting either preferably a certificate of suitability to the relevant monograph on Transmissible Spongiform Encephalopathies of the European Pharmacopoeia, or by the supply of scientific data to substantiate this compliance.

d) Novel excipients:

For excipient(s) used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data, both non-clinical and clinical, shall be provided according to the active substance format previously described.

A document containing the detailed chemical, pharmaceutical and biological information shall be presented. This information shall be formatted in the same order as the section devoted to Active Substance(s) of Module 3.

Information on novel excipient(s) may be presented as a stand-alone document following the format described in the former paragraphs. Where the applicant differs from the novel excipient manufacturer the said stand-alone document shall be made available to the applicant for submission to the competent authority.

Additional information on toxicity studies with the novel excipient shall be provided in Module 4 of the dossier.

Clinical studies shall be provided in Module 5.

3.2.2.5. Control of the finished medicinal product

For the control of the finished medicinal product, a batch of a medicinal product is an entity which comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time.

Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product shall not exceed ± 5 % at the time of manufacture.

Detailed information on the specifications, (release and shelf life) justification for their choice, methods of analysis and their validation shall be provided.

3.2.2.6. Reference standards or materials

Reference preparations and standards used for testing of the finished medicinal product shall be identified and described in detail, if not previously provided in the section related to the active substance.

3.2.2.7. Container and closure of the finished medicinal product

A description of the container and the closure system(s) including the identity of each immediate packaging material and their specifications shall be provided. The specifications shall include description and identification. Non-pharmacopoeial methods (with validation) shall be included where appropriate.

For non-functional outer packaging materials only a brief description shall be provided. For functional outer packaging materials additional information shall be provided.

3.2.2.8. Stability of the finished medicinal product

a) The types of studies conducted, protocols used, and the results of the studies shall be summarised;

b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format; in the case of vaccines, information on cumulative stability shall be provided where appropriate;

c) The post-authorisation stability protocol and stability commitment shall be provided.

4. MODULE 4: NON-CLINICAL REPORTS

4.1. The general outline of Module 4 is as follows:

- Table of contents
- Study reports
  - *Pharmacology*
    - Primary Pharmaco-dynamics
    - Secondary Pharmaco-dynamics
    - Safety Pharmacology
    - Pharmaco-dynamic Interactions
  - *Pharmaco-kinetics*
    - Analytical Methods and Validation Reports

- Absorption
- Distribution
- Metabolism
- Excretion
- Pharmaco-kinetic Interactions (non-clinical)
- Other Pharmaco-kinetic Studies Interactions

– *Toxicology*

- Single-Dose Toxicity
- Repeat-Dose Toxicity Interactions
- Genotoxicity
  - *In vitro*
  - *In vivo* (including supportive toxico-kinetics evaluations) Interactions
- Carcinogenicity
  - Long-term studies
  - Short- or medium-term studies
  - Other studies Interactions

- Reproductive and Developmental Toxicity
    - Fertility and early embryonic development
    - Embryo-fetal development
    - Prenatal and postnatal development
    - Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
- Local Tolerance Interactions

- *Other Toxicity Studies*
    - Antigenicity
    - Immuno-toxicity
    - Mechanistic studies
    - Dependence
    - Metabolites
    - Impurities
    - Other

- Literature references

4.2. Content: basic principles and requirements

Special attention shall be paid to the following selected elements.

(1) The pharmacological and toxicological tests must show:

a) the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings; these should be evaluated in relation to the pathological condition concerned;

b) the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in human beings. All results must be reliable and of general applicability. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results.

Additionally, it is necessary for clinicians to be given information about the therapeutic and toxicological potential of the product.

(2) For biological medicinal products such as immunological medicinal products and medicinal products derived from human blood or plasma, the requirements of this Module may have to be adapted for individual products; therefore the testing program carried out shall be justified by the applicant.

In establishing the testing program, the following shall be taken into consideration:

– all tests requiring repeated administration of the product shall be designed to take account of the possible induction of, and interference by, antibodies;

– examination of reproductive function, of embryo/foetal and peri-natal toxicity, of mutagenic potential and of carcinogenic potential shall be considered. Where constituents other than the active substance(s) are incriminated, validation of their removal may replace the study.

(3) The toxicology and pharmaco-kinetics of an excipient used for the first time in the pharmaceutical field shall be investigated.

(4) Where there is a possibility of significant degradation during storage of the medicinal product, the toxicology of degradation products must be considered.

4.2.1. *Pharmacology*

Pharmacology study shall follow two distinct lines of approach.

– Firstly, the actions relating to the proposed therapeutic use shall be adequately investigated and described. Where possible, recognised and validated assays, both *in vivo* and *in vitro*, shall be used. Novel experimental techniques must be described in such detail as to allow them to be reproduced. The results shall be expressed in quantitative terms using, for example, dose-effect curves, time-effect curves, etc. Wherever possible, comparisons shall be made with data relating to a substance or substances with a similar therapeutic action.

– Secondly, the applicant shall investigate the potential undesirable pharmaco-dynamic effects of the substance on physiological functions. These investigations shall be performed at exposures in the anticipated therapeutic range and above. The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must establish their validity. Any suspected modification of responses resulting from repeated administration of the substance shall be investigated.

For the pharmaco-dynamic medicinal product interaction, tests on combinations of active substances may be prompted either by pharmacological premises or by indications of therapeutic effect. In the first case, the pharmaco-dynamic study shall demonstrate those interactions, which might make the combination of value in therapeutic use. In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall at least be investigated.

4.2.2. *Pharmaco-kinetics*

Pharmaco-kinetics means the study of the fate of the active substance, and its metabolites, within the organism, and covers the study of the absorption, distribution, metabolism (bio-transformation) and excretion of these substances.

The study of these different phases may be carried mainly by means of physical, chemical or possibly by biological methods, and by observation of the actual pharmaco-dynamic activity of the substance itself.

Information on distribution and elimination shall be necessary in all cases where such data are indispensable to determine the dosage for humans, and in respect of chemo-therapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmaco-dynamic effects (e.g. numerous diagnostic agents, etc.).

In vitro studies also can be carried out with the advantage of using human material for comparison with animal material (i.e. protein binding, metabolism, drug-drug interaction).

Pharmaco-kinetic investigation of all pharmacologically active substances is necessary. In the case of new combinations of known substances, which have been investigated in accordance with the provisions of this Directive, pharmaco-kinetic studies may not be required, if the toxicity tests and therapeutic experimentation justify their omission.

The pharmaco-kinetic program shall be designed to allow comparison and extrapolation between animal and human.

4.2.3. *Toxicology*

a) Single-dose toxicity

A single-dose toxicity test shall mean a qualitative and quantitative study of the toxic reactions, which may result from a single administration of the active substance or substances contained in the medicinal product, in the proportions and physico-chemical state in which they are present in the actual product.

The single-dose toxicity test must be carried out in accordance with the relevant guidelines published by the Agency.

b) Repeat-dose toxicity interactions

Repeated dose toxicity tests are intended to reveal any physiological and/or anatomo-pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

Generally, it is desirable that two tests be performed: one short term, lasting two to four weeks, the other long-term. The duration of the latter shall depend on the conditions of clinical use. Its purpose is to describe potential adverse effects to which attention should be paid in clinical studies. The duration is defined in the relevant guidelines published by the Agency.

c) Geno-toxicity

The purposes of the study of mutagenic and clastogenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells. Mutagenic substances may present a hazard to health since exposure to a mutagen carries the risk of inducing germ-line mutation, with the possibility of inherited disorders, and the risk of somatic mutations including those leading to cancer. These studies are obligatory for any new substance.

d) Carcino-genicity

Tests to reveal carcinogenic effects shall normally be required:

1. These studies shall be performed for any medicinal product whose expected clinical use is for a prolonged period of a patient's life, either continuously or repeatedly in an intermittent manner.

2. These studies are recommended for some medicinal products if there is concern about their carcinogenic potential, e.g. from product of the same class or similar structure, or from evidence in repeated dose toxicity studies.

3. Studies with unequivocally geno-toxic compounds are not needed, as they are presumed to be trans-species carcinogens, implying a hazard to humans. If such a medicinal product is intended to be administered chronically to humans a chronic study may be necessary to detect early tumorigenic effects.

e) Reproductive and developmental toxicity

Investigation of possible impairment of male or female reproductive function as well as harmful effects on progeny shall be performed by appropriate tests.

These tests comprise studies of effect on adult male or female reproductive function, studies of the toxic and teratogenic effects at all stages of development from conception to sexual maturity as well as latent effects, when the medicinal product under investigation has been administered to the female during pregnancy.

Omission of these tests must be adequately justified.

Depending on the indicated use of the medicinal product, additional studies addressing development when administering the medicinal product of the offspring may be warranted.

Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent. Peri- and postnatal studies shall be conducted in at least one species. If the metabolism of a medicinal product in particular species is known to be similar to that in man, it is desirable to include this species. It is also desirable that one of the species is the same as in the repeated dose toxicity studies.

The state of scientific knowledge at the time when the application is lodged shall be taken into account when determining the study design.

f) Local tolerance

The purpose of local tolerance studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body, which may come into contact with the medicinal product as a result of its administration in clinical use. The testing strategy shall be such that any mechanical effects of administration or purely physico-chemical actions of the product can be distinguished from toxicological or pharmaco-dynamic ones.

Local tolerance testing shall be conducted with the preparation being developed for human use, using the vehicle and/or excipients in treating the control group(s). Positive controls/reference substances shall be included where necessary.

The design of local tolerance tests (choice of species, duration, frequency and route of administration, doses) will depend upon the problem to be investigated and the proposed conditions of administration in clinical use. Reversibility of local lesions shall be performed where relevant.

Studies in animals can be substituted by validated *in vitro* tests provided that the test results are of comparable quality and usefulness for the purpose of safety evaluation.

For chemicals applied to the skin (e.g. dermal, rectal, vaginal), the sensitising potential shall be evaluated in at least one of the test systems currently available (the guinea pig assay or the local lymph node assay).

5. MODULE 5: CLINICAL STUDY REPORTS

5.1. Format and Presentation

The general outline of Module 5 is as follows:

- Table of contents for clinical study reports
- Tabular listing of all clinical studies
- Clinical study reports
  - *Reports of Bio-pharmaceutical Studies*
    - Bio-availability Study Reports
    - Comparative Bio-availability and Bio-equivalence Study Reports
    - In vitro – In vivo Correlation Study Report
    - Reports of Bio-analytical and Analytical Methods
  - *Reports of Studies Pertinent to Pharmaco-kinetics Using Human Bio-materials*
    - Plasma Protein Binding Study Reports
    - Reports of Hepatic Metabolism and Interaction Studies
    - Reports of Studies Using Other Human Bio-materials Methods

– *Reports of Human Pharmaco-kinetic Studies*

  – Healthy subjects Pharmaco-kinetics and Initial Tolerability Study Reports

  – Patient Pharmaco-kinetics and Initial Tolerability Study Reports

  – Intrinsic Factor Pharmaco-kinetics Study Reports

  – Extrinsic Factor Pharmaco-kinetics Study Reports

  – Population Pharmaco-kinetics Study Reports Methods

– *Reports of Human Pharmaco-dynamic Studies*

  – Healthy Subject Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Study Reports

  – Patient Pharmaco-dynamic and Pharmaco-kinetics/Pharmaco-dynamic Studies Study Reports Methods

– *Reports of Efficacy and Safety Studies*

  – Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

  – Study Reports of Uncontrolled Clinical Studies

– Reports of Analyses of Data from More than One Study including any formal integrated analyses, meta-analyses and bridging analyses

– Other Study Reports Methods

– *Reports of Post-marketing Experience*

– Literature references Methods

5.2 Content: basic principles and requirements

Special attention shall be paid to the following selected elements.

a) The clinical particulars to be provided pursuant to Article 10(1) and point (12) of Annex I must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorisation. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favourable and unfavourable.

b) Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals in accordance with the requirements of Module 4 of this Annex. The investigator must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him at least with the investigator's brochure, consisting of all the relevant information known prior to the onset of a clinical trial including chemical, pharmaceutical and biological data, toxicological, pharmaco-kinetic and pharmaco-dynamic data in animals and the results of earlier clinical trials, with adequate data to justify the nature, scale and duration of the proposed trial; the complete pharmacological and toxicological reports shall be provided on request. For materials of human or animal origin, all available means shall be employed to ensure safety from transmission of infectious agents prior to the commencement of the trial.

c) Marketing authorisation holders must arrange for essential clinical trial documents (including case report forms) other than subject's medical files, to be kept by the owners of the data:

– for at least 15 years after completion or discontinuation of the trial,

– or for at least two years after the granting of the last marketing authorisation in the Union and when there are no pending or contemplated marketing applications in the Union,

– or for at least two years after formal discontinuation of clinical development of the investigational product.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor. It is the responsibility of the sponsor to inform the hospital, institution or practice as to when these documents no longer need to be retained.

The sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorised. This documentation shall include: the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product, the reference medicinal product and/or the placebo used; standard operating procedures; all written opinions on the protocol and procedures; the investigator's brochure; case report forms on each trial subject; final report; audit certificate(s), if available. The final report shall be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorised.

In addition for trials conducted within the Union, the marketing authorisation holder shall make any additional arrangements for archiving of documentation in accordance with Regulation (EU) No 536/2014 and implementing detailed guidelines.

Any change of ownership of the data shall be documented.

All data and documents shall be made available if requested by relevant authorities.

d) The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made:

– the protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational medicinal product used;

– audit certificate(s), if available;

– the list of investigator(s), and each investigator shall give his name, address, appointments, qualifications and clinical duties, state where the trial was carried out and assemble the information in respect of each patient individually, including case report forms on each trial subject;

– final report signed by the investigator and for multi-centre trials, by all the investigators or the co-ordinating (principal) investigator.

e) The particulars of clinical trials referred to in point (d) shall be forwarded to the competent authorities. However, in agreement with the competent authorities, the applicant may omit part of this information. Complete documentation shall be provided forthwith upon request.

The investigator shall, in his conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its tolerance, its efficacy and any useful information relating to indications and contra-indications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of over dosage. In reporting the results of a multi-centre study, the principal investigator shall, in his conclusions, express an opinion on the safety and efficacy of the investigational medicinal product on behalf of all centres.

f) The clinical observations shall be summarised for each trial indicating:

1) the number and sex of subjects treated;

2) the selection and age-distribution of the groups of patients being investigated and the comparative tests;

3) the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;

4) where controlled trials were carried out under the above conditions, whether the control group:

– received no treatment

– received a placebo

– received another medicinal product of known effect

– received treatment other than therapy using medicinal products

5) the frequency of observed adverse reactions;

6) details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstruation, or whose physiological or pathological condition requires special consideration;

7) parameters or evaluation criteria of efficacy and the results in terms of these parameters;

8) a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.

g) In addition, the investigator shall always indicate his observations on:

1) any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;

2) any interactions that have been observed with other medicinal products administered concomitantly;

3) the criteria determining exclusion of certain patients from the trials;

4) any deaths which occurred during the trial or within the follow-up period.

h) Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.

i) Total or partial omission of data must be explained. Should unexpected results occur during the course of the trials, further pre clinical toxicological and pharmacological tests must be undertaken and reviewed.

j) If the medicinal product is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration, as well as the establishment of long-term dosage.

5.2.1. *Reports of bio-pharmaceutics studies*

Bio-availability study reports, comparative bio-availability, bio-equivalence study reports, reports on *in vitro* and *in vivo* correlation study, and bio-analytical and analytical methods shall be provided.

In addition, an assessment of bio-availability shall be undertaken where necessary to demonstrate bio-equivalence for the medicinal products referred to in Article 10(1) (a) of Directive 2001/83/EC in its original version.

5.2.2. *Reports of studies pertinent to pharmaco-kinetics using human bio-materials*

For the purposes of this Annex, human bio-materials shall mean any proteins, cells, tissues and related materials derived from human sources that are used *in vitro* or *ex vivo* to assess pharmaco-kinetics properties of drug substances.

In this respect, reports of plasma protein binding study, hepatic metabolism and active substance interaction studies and studies using other human bio-materials shall be provided.

5.2.3. *Reports of human pharmaco-kinetic studies*

a) The following pharmaco-kinetic characteristics shall be described:

– absorption (rate and extent),

– distribution,

– metabolism,

– excretion.

Clinically significant features including the implication of the kinetic data for the dosage regimen especially for patients at risk, and differences between man and animal species used in the pre clinical studies, shall be described.

In addition to standard multiple-sample pharmaco-kinetics studies, population pharmaco-kinetics analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose- pharmaco-kinetics response relationship. Reports of pharmaco-kinetic and initial tolerability studies in healthy subjects and in patients, reports of pharmaco-kinetic studies to assess effects of intrinsic and extrinsic factors, and reports of population pharmaco-kinetic studies shall be provided.

b) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmaco-kinetic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.4. *Reports of human pharmaco-dynamic studies*

a) The pharmaco-dynamic action correlated to the efficacy shall be demonstrated including:

– the dose-response relationship and its time course,

– justification for the dosage and conditions of administration,

– the mode of action, if possible.

The pharmaco-dynamic action not related to efficacy shall be described.

The demonstration of pharmaco-dynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect.

b) If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmaco-dynamic interactions between the active substance and other medicinal products or substances shall be investigated.

5.2.5. *Reports of efficacy and safety studies*

5.2.5.1. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

In general, clinical trials shall be done as 'controlled clinical trials' if possible, randomised and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven therapeutic value rather than with the effect of a placebo.

(1) As far as possible, and particularly in trials where the effect of the product cannot be objectively measured, steps shall be taken to avoid bias, including methods of randomisation and blinding.

(2) The protocol of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures taken to avoid bias, particularly methods of randomisation, shall be documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.

The safety data shall be reviewed taking into account guidelines published by the Commission, with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths. Any patients or patient groups at increased risk shall be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of metabolism or excretion etc. The implication of the safety evaluation for the possible uses of the medicinal product shall be described.

5.2.5.2. Study reports of uncontrolled clinical studies reports of analyses of data from more than one study and other clinical study reports

These reports shall be provided.

5.2.6. *Reports of post-marketing experience*

If the medicinal product is already authorised in third countries, information shall be given in respect of adverse reactions of the medicinal product concerned and medicinal products containing the same active substance(s), in relation to the usage rates if possible.

5.2.7. *Case reports forms and individual patient listings*

When submitted in accordance with the relevant Guideline published by the Agency, case report forms and individual patient data listings shall be provided and presented in the same order as the clinical study reports and indexed by study.

PART II

SPECIFIC MARKETING AUTHORISATION DOSSIERS AND REQUIREMENTS

Some medicinal products present specific features which are such that all the requirements of the marketing authorisation application dossier as laid down in Part I of this Annex need to be adapted. To take account of these particular situations, an appropriate and adapted presentation of the dossier shall be followed by applicants.

1. WELL-ESTABLISHED MEDICINAL USE

For medicinal products the active substance(s) of which has/have a 'well-established medicinal use' as referred to Article 14 with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.

The applicant shall submit Modules 1, 2 and 3 as described in part I of this Annex.

For Modules 4 and 5, a detailed scientific bibliography shall address non-clinical and clinical characteristics.

The following specific rules shall apply in order to demonstrate the well-established medicinal use:

a) Factors which have to be taken into account in order to establish a well-established medicinal use of constituents of medicinal products are:

– the time over which a substance has been used,

– quantitative aspects of the use of the substance,

– the degree of scientific interest in the use of the substance (reflected in the published scientific literature), and

– the coherence of scientific assessments.

Therefore different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing a well-established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Union.

b) The documentation submitted by the applicant should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable and unfavourable, must be communicated. With respect to the provisions on ‘well-established medicinal use’ it is in particular necessary to clarify that ‘bibliographic reference’ to other sources of evidence (post marketing studies, epidemiological studies, etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.

c) Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking.

d) The non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.

e) Post-marketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue.

2. ESSENTIALLY SIMILAR MEDICINAL PRODUCTS

a) Applications based upon Article 10(1)(a)(i) of Directive 2001/83/CE in its original version (essentially similar products) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex provided the applicant has been granted the consent of the holder of the original marketing authorisation to cross refer to the content of his Modules 4 and 5.

b) Applications based upon Article 10(1)(a)(iii) of Directive 2001/83/CE in its original version (essentially similar products i.e. generics) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex together with data showing bio-availability and bio-equivalence with the original medicinal product provided the latter is not a biological medicinal product (see Part II, 4 Similar biological medicinal products).

For these products the non-clinical/clinical overviews/summaries shall particularly focus on the following elements:

– the grounds for claiming essential similarity;

– a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed together with an evaluation of these impurities;

– an evaluation of the bio-equivalence studies or a justification why studies were not performed with respect to the guideline on 'Investigation of Bio-availability and Bio-equivalence';

– an update of published literature relevant to the substance and the present application. It may be acceptable for articles in 'peer review' journals to be annotated for this purpose;

– every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non-clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.

– if applicable, additional data in order to demonstrate evidence on the equivalence of safety and efficacy properties of different salts, esters or derivatives of an authorised active substance should be provided by the applicant when he claims essential similarity.

3. ADDITIONAL DATA REQUIRED IN SPECIFIC SITUATIONS

Where the active substance of an essentially similar medicinal product contains the same therapeutic moiety as the original authorised product associated with a different salt/ester complex/derivative evidence that there is no change in the pharmaco-kinetics of the moiety, pharmaco-dynamics and/or in toxicity which could change the safety/efficacy profile shall be demonstrated. Should this not be the case, this association shall be considered as a new active substance.

Where a medicinal product is intended for a different therapeutic use or presented in a different pharmaceutical form or to be administered by different routes or in different doses or with a different posology, the results of appropriate toxicological and pharmacological tests and/or of clinical trials shall be provided.

4. BIOSIMILAR MEDICINAL PRODUCTS

The provisions of Article 10(1)(a)(iii) of Directive 2001/83/CE in its original version may not be sufficient in the case of biological medicinal products. If the information required in the case of essentially similar products (generics) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided.

When a biological medicinal product as defined in Article 5(1), point (14), which refers to an original medicinal product having been granted a marketing authorisation in the Union, is submitted for a marketing authorisation by an independent applicant after the expiry of data protection period, the following approach shall be applied:

– Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.

– Due to the diversity of biological medicinal products, the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product.

The general principles to be applied are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency. In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.

5. FIXED-DOSE COMBINATION MEDICINAL PRODUCTS

Applications based upon Article 10(1)(b) of Directive 2001/83/CE in its original version shall relate to new medicinal products made of at least two active substances not previously authorised as a fixed-dose combination medicinal product.

For those applications a full dossier (Modules 1 to 5) shall be provided for the fixed combination medicinal product. Where applicable, information regarding the manufacturing sites and the adventitious agents, safety evaluation shall be provided.

6. DOCUMENTATION FOR APPLICATIONS IN EXCEPTIONAL CIRCUMSTANCES

When, as provided for in Article 48(1) and (2), the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

– the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or

– in the present state of scientific knowledge, comprehensive information cannot be provided, or

– it would be contrary to generally accepted principles of medical ethics to collect such information,

marketing authorisation may be granted subject to certain specific obligations.

These obligations may include the following:

– the applicant shall complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile,

– the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorised person,

– the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

7. MIXED MARKETING AUTHORISATION APPLICATIONS

Mixed marketing-authorisation applications shall mean marketing-authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references. All other Module(s) are in accordance with the structure described in Part I of this Annex. The competent authority shall accept the proposed format presented by the applicant on a case by case basis.

PART III

PARTICULAR MEDICINAL PRODUCTS

This Part lays down specific requirements related to the nature of identified medicinal products.

1. BIOLOGICAL MEDICINAL PRODUCTS

1.1. Plasma-derived medicinal product

For medicinal products derived from human blood or plasma and by derogation from the provisions of Module 3, the dossier requirements mentioned in 'Information related to the starting and raw materials', for starting materials made of human blood/plasma may be replaced by a Plasma Master File certified in accordance with this Part.

a) Principles

For the purposes of this Annex:

– Plasma Master File shall mean a stand-alone documentation, which is separate from the dossier for marketing authorisation which provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipient and active substance(s), which are part of medicinal products or medical devices referred to in Regulation (EU) 2017/745.

– Every centre or establishment for fractionation/processing of human plasma shall prepare and keep updated the set of detailed relevant information referred to in the Plasma Master File.

– The Plasma Master File shall be submitted to the Agency or to the competent authority by the applicant for a marketing authorisation or the holder of the marketing authorisation. Where the applicant for a marketing authorisation or the marketing authorisation holder differs from the holder of the Plasma Master File, the Plasma Master File shall be made available to the applicant or marketing authorisation holder for submission to the competent authority. In any case, the applicant or marketing authorisation holder shall take responsibility for the medicinal product.

– The competent authority that is evaluating the marketing authorisation shall await for the Agency to issue the certificate before deciding on the application.

– Any marketing authorisation dossier containing a human plasma-derived constituent shall refer to the Plasma Master File corresponding to the plasma used as a starting/raw material.

b) Content

In accordance with Regulation (EU) 2024/1938, which refers to the requirements for donors and the testing of donations, the Plasma Master File shall include information on the plasma used as starting/raw material, in particular:

(1) Plasma origin

(i) information on centres or establishments in which blood/plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections.

(ii) information on centres or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status.

(iii) selection/exclusion criteria for blood/plasma donors.

(iv) system in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished products and vice versa.

(2) Plasma quality and safety

(i) compliance with European Pharmacopoeia Monographs.

(ii) testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests used.

(iii) technical characteristics of bags for blood and plasma collection, including information on anticoagulants solutions used.

(iv) conditions of storage and transport of plasma.

(v) procedures for any inventory hold and/or quarantine period.

(vi) characterisation of the plasma pool.

(3) System in place between the plasma-derived medicinal product manufacturer and/or plasma fractionator/processor on the one hand, and blood/plasma collection and testing centres or establishments on the other hand, which defines the conditions of their interaction and their agreed specifications.

In addition, the Plasma Master File shall provide a list of the medicinal products for which the Plasma Master File is valid, whether the medicinal products have been granted a marketing authorisation or are in the process of being granted such an authorisation, including medicinal products referred to in Article 2 of Regulation (EU) No 536/2014.

c) Evaluation and Certification

– For medicinal products not yet authorised, the marketing authorisation applicant shall submit a full dossier to a competent authority, which shall be accompanied by a separate Plasma Master File where one does not already exist.

– The Plasma Master File is subject to a scientific and technical evaluation carried out by the Agency. A positive evaluation shall result in a certificate of compliance with Union legislation for the Plasma Master File, which shall be accompanied by the evaluation report. The certificate issued shall apply throughout the Union.

– The Plasma Master File shall be updated and re-certified on an annual basis.

– Changes subsequently introduced to the terms of a Plasma Master File must follow evaluation procedure laid down by Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of a marketing authorisation falling within the scope of Regulation (EU) 2026/…[+]. Conditions for the assessment of these changes are laid down by Regulation (EC) No 1234/2008.

– As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Plasma Master File on the concerned medicinal product(s).

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

– By derogation from the provisions of the second indent of this point (evaluation and certification), where a Plasma Master File corresponds only to blood/plasma-derived medicinal products the marketing authorisation of which is restricted to a single Member State, the scientific and technical evaluation of the said Plasma Master File shall be carried out by the national competent authority of that Member State.

1.2. Vaccines

For vaccines for human use and by derogation from the provisions of Module 3 on 'Active substance(s)', the following requirements when based on the use of a Vaccine Antigen Master File system shall apply.

The marketing authorisation application dossier of a vaccine other than human influenza vaccine, shall be required to include a Vaccine Antigen Master File for every vaccine antigen that is an active substance of this vaccine.

a) Principles

For the purposes of this Annex:

– Vaccine Antigen Master File shall mean a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information of biological, pharmaceutical and chemical nature concerning each of the active substances, which are part of this medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorisation holder.

– A vaccine may contain one or several distinct vaccine antigens. There are as many active substance(s) as vaccine antigen(s) present in a vaccine.

– A combined vaccine contains at least two distinct vaccine antigens aimed at preventing a single or several infectious diseases.

– A monovalent vaccine is a vaccine, which contains one vaccine antigen aimed at preventing a single infectious disease.

b) Content

The Vaccine Antigen Master File shall contain the following information extracted from the relevant part (Active substance) of Module 3 on 'Quality Data' as delineated in Part I of this Annex:

Active Substance

1. General Information, including compliance with the relevant monograph(s) of the European Pharmacopoeia.

2. Information on the manufacture of the active substance: this heading must cover the manufacturing process, information on the starting and raw materials, specific measures on TSEs and adventitious agents safety evaluation and facilities and equipment.

3. Characterisation of the active substance

4. Quality control of the active substance

5. Reference standard and materials

6. Container and closure system of the active substance

7. Stability of the active substance.

c) Evaluation and Certification

– For novel vaccines, which contain a novel vaccine antigen, the applicant shall submit to a competent authority a full marketing-authorisation application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen that is part of the novel vaccine where no master file already exists for the single vaccine antigen. A scientific and technical evaluation of each Vaccine Antigen Master File shall be carried out by the Agency. A positive evaluation shall result in a certificate of compliance to the European legislation for each Vaccine Antigen Master File, which shall be accompanied by the evaluation report. The certificate shall apply throughout the Union.

– The provisions of the first indent shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of these vaccine antigens are part of vaccines already authorised in the Union.

– Changes to the content of a Vaccine Antigen Master File for a vaccine authorised in the Union shall be subject to a scientific and technical evaluation carried out by the Agency in accordance with the procedure laid down in Regulation (EC) No 1234/2008. In the case of a positive evaluation the Agency shall issue a certificate of compliance with Union legislation for the Vaccine Antigen Master File. The certificate issued shall apply throughout the Union.

– By derogation from the provisions of the first, second and third indents of this point (evaluation and certification), where a Vaccine Antigen Master File corresponds only to a vaccine which is the subject of a marketing authorisation which has not been/will not be granted according to a Union procedure, and, provided the authorised vaccine includes vaccine antigens which have not been evaluated through a Union procedure, the scientific and technical evaluation of the said Vaccine Antigen Master File and its subsequent changes, shall be carried out by the national competent authority that has granted the marketing authorisation.

– As a second step to the provisions in the first, second, third and fourth indents, the competent authority that will grant or has granted the marketing authorisation shall take into account the certification, re-certification or variation of the Vaccine Antigen Master File on the concerned medicinal product(s).

2. RADIOPHARMACEUTICALS AND PRECURSORS

2.1. Radiopharmaceuticals

For the purposes of this chapter, applications based upon Article 17(1) and point (22) of Annex I shall provide a full dossier in which the following specific details shall be included:

Module 3

a) In the context of a radiopharmaceutical kit, which is to be radio-labelled after supply by the manufacturer, the active substance is considered to be that part of the formulation which is intended to carry or bind the radionuclide. The description of the manufacturing method of radiopharmaceutical kits shall include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product. The necessary specifications of the radionuclide shall be described in accordance, where relevant, with the general monograph or specific monographs of the European Pharmacopoeia. In addition, any compounds essential for the radio-labelling shall be described. The structure of the radio-labelled compound shall also be described.

For radionuclides, the nuclear reactions involved shall be discussed.

In a generator, both mother and daughter radionuclides shall be considered as active substances.

b) Details of the nature of the radionuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be provided.

c) Starting materials include irradiation target materials.

d) Considerations on chemical/radiochemical purity and its relationship to bio-distribution shall be provided.

e) Radio-nuclide purity, radiochemical purity and specific activity shall be described.

f) For generators, details on the testing for mother and daughter radionuclides are required. For generator-eluates, tests for mother radionuclides and for other constituents of the generator system shall be provided.

g) The requirement to express the content of active substances in terms of the mass of active entities shall only apply to radio-pharmaceutical kits. For radionuclides, radioactivity shall be expressed in Becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.

h) For kits, the specifications of the finished product shall include tests on performance of products after radio-labelling. Appropriate controls on radiochemical and radionuclidic purity of the radio-labelled compound shall be included. Any material essential for radio-labelling shall be identified and assayed.

i) Information on stability shall be given for radionuclide generators, radionuclide kits and radio-labelled products. The stability during use of radiopharmaceuticals in multi-dose vials shall be documented.

Module 4

It is appreciated that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radiopharmaceuticals; in therapy, it is the property desired. The evaluation of safety and efficacy of radiopharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognised system by a particular route of administration.

Module 5

The results of clinical trials shall be provided where applicable otherwise justified in the clinical overviews.

2.2. Radiopharmaceutical precursors for radio-labelling purposes

In the specific case of a radiopharmaceutical precursor intended solely for radio-labelling purposes, the primary objective shall be to present information which would address the possible consequences of poor radio-labelling efficiency or *in vivo* dissociation of the radio-labelled conjugate, i.e. questions related to the effects produced in the patient by free radionuclide. In addition, it is also necessary to present relevant information relating to occupational hazards, i.e. radiation exposure to hospital staff and to the environment.

In particular, the following information where applicable shall be provided:

Module 3

The provisions of Module 3 shall apply to the registration of radiopharmaceutical precursors as defined above (points a) to i)), where applicable.

Module 4

Concerning single dose and repeat dose toxicity, the results of studies carried out in conformity with the provisions related to good laboratory practice laid down in Directives 2004/9/EC and 2004/10/EC shall be provided, unless otherwise justified.

Mutagenicity studies on the radionuclide are not considered to be useful in this particular case.

Information relating to the chemical toxicity and disposition of the relevant 'cold' nuclide shall be presented.

Module 5

Clinical information generated from clinical studies using on the precursor itself is not considered to be relevant in the specific case of a radiopharmaceutical precursor intended solely for radio-labelling purposes.

However, information demonstrating the clinical utility of the radiopharmaceutical precursor when attached to relevant carrier molecules shall be presented.

3. HOMEOPATHIC MEDICINAL PRODUCTS

This section sets out specific provisions on the application of Modules 3 and 4 to homeopathic medicinal products as defined in Article 5(1), point (67).

Module 3

The provisions of Module 3 shall apply to the documents submitted in accordance with Article 131(2), in the simplified registration of homeopathic medicinal products referred to in Article 130(1) as well as to the documents for authorisation of other homeopathic medicinal products referred to in) Article 137(1) with the following modifications.

a) Terminology

The Latin name of the homeopathic stock described in the marketing authorisation application dossier must be in accordance with the Latin title of the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State. Where relevant the traditional name(s) used in each Member State shall be provided.

b) Control of starting materials

The particulars and documents on the starting materials, i.e. all of the materials used including raw materials and intermediates up to the final dilution to be incorporated into the finished medicinal product, accompanying the application shall be supplemented by additional data on the homeopathic stock.

The general quality requirements shall apply to all of the starting and raw materials as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished medicinal product. If possible, an assay is required if toxic components are present and if the quality cannot be controlled on final dilution to be incorporated because of the high dilution degree. Every step of the manufacturing process from the starting materials up to the final dilution to be incorporated into the finished medicinal product must be fully described.

In case dilutions are involved, these dilution steps should be done in accordance with the homeopathic manufacturing methods laid down in the relevant monograph of the European Pharmacopoeia or, in absence thereof, by an official pharmacopoeia of a Member State.

c) Control tests on the finished medicinal product

The general quality requirements shall apply to the homeopathic finished medicinal products, any exception needs to be duly justified by the applicant.

Identification and assay of all the toxicologically relevant constituents shall be carried out. If it can be justified that an identification and/or an assay on all the toxicologically relevant constituents is not possible e.g. due to their dilution in the finished medicinal product the quality shall be demonstrated by complete validation of the manufacturing and dilution process.

d) Stability tests

The stability of the finished medicinal product must be demonstrated. Stability data from the homeopathic stocks are generally transferable to dilutions/triturations obtained thereof. If no identification or assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered.

Module 4

The provisions of Module 4 shall apply to the simplified registration of homeopathic medicinal products referred to in Article 130(1) with the following specifications.

Any missing information must be justified, e.g., justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking.

4. HERBAL MEDICINAL PRODUCTS

Applications for herbal medicinal products shall provide a full dossier in which the following specific details shall be included.

Module 3

The provisions of Module 3, including compliance with monograph(s) of the European Pharmacopoeia, shall apply to the authorisation of herbal medicinal products. The state of scientific knowledge at the time when the application is lodged shall be taken into account.

The following aspects specific to herbal medicinal products shall be considered:

(1) Herbal substances and herbal preparations

For the purposes of this Annex, the terms ‘herbal substances and preparations’ shall be considered equivalent to the terms ‘herbal drugs and herbal drug preparations’, as defined in the European Pharmacopoeia.

With respect to the nomenclature of the herbal substance, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal substance, the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.

With respect to the nomenclature of the herbal preparation, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the parts of the plants, the definition of the herbal preparation, the ratio of the herbal substance to the herbal preparation, the extraction solvent(s), the other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code shall be provided.

To document the section of the structure for herbal substance(s) and herbal preparation(s) where applicable, the physical form, the description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereo-chemistry, the molecular formula, and the relative molecular mass) as well as other constituent(s) shall be provided.

To document the section on the manufacturer of the herbal substance, the name, address, and responsibility of each supplier, including contractors, and each proposed site or facility involved in production/collection and testing of the herbal substance shall be provided, where appropriate.

To document the section on the manufacturer of the herbal preparation, the name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation shall be provided, where appropriate.

With respect to the description of manufacturing process and process controls for the herbal substance, information shall be provided to adequately describe the plant production and plant collection, including the geographical source of the medicinal plant and cultivation, harvesting, drying and storage conditions.

With respect to the description of manufacturing process and process controls for the herbal preparation, information shall be provided to adequately describe the manufacturing process of the herbal preparation, including description of the processing, solvents and reagents, purification stages and standardisation.

With respect to the manufacturing process development, a brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable shall be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the herbal substance(s) and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substance(s) and herbal preparation(s), where applicable, contained as active substance(s) in the herbal medicinal product applied for shall be discussed, where appropriate.

With respect to the elucidation of the structure and other characteristics of the herbal substance, information on the botanical, macroscopical, microscopical, phyto-chemical characterisation, and biological activity if necessary, shall be provided.

With respect to the elucidation of the structure and other characteristics of the herbal preparation, information on the phyto- and physicochemical characterisation, and biological activity if necessary, shall be provided.

The specifications for the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

The analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

With respect to the validation of analytical procedures, analytical validation information, including experimental data for the analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

With respect to batch analyses, description of batches and results of batch analyses for the herbal substance(s) and herbal preparation(s) where applicable shall be provided, including those for pharmacopoeial substances.

Justification for the specifications of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

Information on the reference standards or reference materials used for testing of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

Where the herbal substance or the herbal preparation is the subject of a monograph, the applicant can apply for a certificate of suitability that was granted by the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe.

(2) Herbal Medicinal Products

With respect to the formulation development, a brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phyto-chemical composition of the products used in supporting bibliographic data and the herbal medicinal product applied for shall be discussed, where appropriate.

5. ORPHAN MEDICINAL PRODUCTS

– In the case of an orphan medicinal product in the meaning of Regulation (EU) 2026/…[+], general provisions of Part II-6 (exceptional circumstances) can be applied. The applicant shall then justify in the non-clinical and clinical summaries the reasons for which it is not possible to provide the complete information and shall provide a justification of the benefit/risk balance for the orphan medicinal product concerned.

– When an applicant for a marketing authorisation for an orphan medicinal product invokes the provisions of Article 14 and Part II-1 of this Annex (well-established medicinal use), the systematic and documented use of the concerned substance can refer – as way of derogation – to the use of that substance in accordance with the provisions of Article 4(1), (4), (5) and (6) of this Directive.

PART IV
ADVANCED THERAPY MEDICINAL PRODUCTS

1. INTRODUCTION

Marketing authorisation applications for advanced therapy medicinal products, as defined in Article 5(1), point (8), shall follow the format requirements (Modules 1, 2, 3, 4 and 5) described in Part I of this Annex.

[+] OJ: please insert in the text the number of the Regulation in document PE-CONS 65/26 (2023/0131(COD)).

The technical requirements for Modules 3, 4 and 5 for biological medicinal products, as described in Part I of this Annex, shall apply. The specific requirements for advanced therapy medicinal products described in sections 3, 4 and 5 of this part explain how the requirements in Part I apply to advanced therapy medicinal products. In addition, where appropriate and taking into account the specificities of advanced therapy medicinal products, additional requirements have been set.

Due to the specific nature of advanced therapy medicinal products, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorisation application, in accordance with the scientific guidelines relating to the quality, safety and efficacy of medicinal products referred to in point 4 of the 'Introduction and general principles'.

The risk analysis may cover the entire development. Risk factors that may be considered include: the origin of the cells (autologous, allogeneic, xenogeneic), the ability to proliferate and/or differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the nature of the gene therapy medicinal products, the extent of replication competence of viruses or micro-organisms used *in vivo*, the level of integration of nucleic acids sequences or genes into the genome, the long-time functionality, the risk of oncogenicity and the mode of administration or use.

Relevant available non-clinical and clinical data or experience with other, related advanced therapy medicinal products may also be considered in the risk analysis.

Any deviation from the requirements of this Annex shall be scientifically justified in Module 2 of the application dossier. The risk analysis described above, when applied, shall also be included and described in Module 2. In this case, the methodology followed, the nature of the identified risks and the implications of the risk-based approach for the development and evaluation program shall be discussed and any deviations from the requirements of this Annex resulting from the risk analysis shall be described.

2. DEFINITIONS

For the purposes of this Annex, the definitions laid down in Regulation (EC) No 1394/2007 shall apply.

3. SPECIFIC REQUIREMENTS REGARDING MODULE 3

3.1. Specific requirements for all advanced therapy medicinal products

A description of the traceability system that the marketing authorisation holder intends to establish and maintain to ensure that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used, shall be provided.

The traceability system shall be complementary to, and compatible with, the requirements established in Regulation (EU) 2024/1938.

3.2. Specific requirements for gene therapy medicinal products

3.2.1. *Introduction: finished product, active substance and starting materials*

3.2.1.1. Gene therapy medicinal product containing recombinant nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es)

The finished medicinal product shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es) formulated in their final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.

The active substance shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es).

3.2.1.2. Gene therapy medicinal product containing genetically modified cells

The finished medicinal product shall consist of genetically modified cells formulated in the final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.

The active substance shall consist of cells genetically modified by one of the products described in section 3.2.1.1 above.

3.2.1.3. In the case of products consisting of viruses or viral vectors, the starting materials shall be the components from which the viral vector is obtained, i.e. the master virus vector seed or the plasmids used to transfect the packaging cells and the master cell bank of the packaging cell line.

3.2.1.4. In the case of products consisting of plasmids, non-viral vectors and genetically modified microorganism(s) other than viruses or viral vectors, the starting materials shall be the components used to generate the producing cell, i.e. the plasmid, the host bacteria and the master cell bank of recombinant microbial cells.

3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells. The principles of good manufacturing practice shall apply from the bank system used to produce the vector onwards.

3.2.2. *Specific requirements*

In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the following requirements shall apply:

(a) information shall be provided on all the starting materials used for the manufacture of the active substance, including the products necessary for the genetic modification of human or animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells, taking into consideration the possible absence of purification steps;

(b) for products containing a microorganism or a virus, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the microorganism or virus, pathogenicity and characteristics of the parental strain shall be provided;

(c) process-related impurities and product-related impurities shall be described in the relevant sections of the dossier, and in particular replication competent virus contaminants if the vector is designed to be replication incompetent;

(d) for plasmids, quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product;

(e) for genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent freezing/storage procedures, shall be tested.

For genetically modified cells, in addition to the specific requirements for gene therapy medicinal products, the quality requirements for somatic cell therapy medicinal products and tissue engineered products (see section 3.3) shall apply.

3.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products

3.3.1. *Introduction: finished product, active substance and starting materials*

The finished medicinal product shall consist of the active substance formulated in its immediate container for the intended medical use, and in its final combination for combined advanced therapy medicinal products.

The active substance shall be composed of the engineered cells and/or tissues.

Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) which are combined with manipulated cells of which they form an integral part shall be considered as starting materials, even if not of biological origin.

Materials used during the manufacture of the active substance (e.g. culture media, growth factors) and that are not intended to form part of the active substance shall be considered as raw materials.

3.3.2. *Specific requirements*

In addition to the requirements set out in sections 3.2.1 and 3.2.2 of Part I of this Annex, the following requirements shall apply:

3.3.2.1. Starting materials

(a) Summary information shall be provided on donation, procurement and testing of the human tissue and cells used as starting materials and made in accordance with Regulation (EU) 2024/1938. If non-healthy cells or tissues (e.g. cancer tissue) are used as starting materials, their use shall be justified.

(b) If allogeneic cell populations are being pooled, the pooling strategies and measures to ensure traceability shall be described.

(c) The potential variability introduced through the human or animal tissues and cells shall be addressed as part of the validation of the manufacturing process, characterisation of the active substance and the finished product, development of assays, setting of specifications and stability.

(d) For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), specific acceptance criteria, measures to prevent and monitor infections in the source/donor animals, testing of the animals for infectious agents, including vertically transmitted micro-organisms and viruses, and evidence of the suitability of the animal facilities shall be provided.

(e) For cell-based products derived from genetically modified animals, the specific characteristics of the cells related to the genetic modification shall be described. A detailed description of the method of creation and the characterisation of the transgenic animal shall be provided.

(f) For the genetic modification of the cells, the technical requirements specified in section 3.2 shall apply.

(g) The testing regimen of any additional substance (scaffolds, matrices, devices, biomaterials, biomolecules or other components), which are combined with engineered cells of which they form an integral part, shall be described and justified.

(h) For scaffolds, matrices and devices that fall under the definition of a medical device or active implantable medical device, the information required under section 3.4 for the evaluation of the combined advanced therapy medicinal product shall be provided.

3.3.2.2. Manufacturing process

(a) The manufacturing process shall be validated to ensure batch and process consistency, functional integrity of the cells throughout manufacturing and transport up to the moment of application or administration, and proper differentiation state.

(b) If cells are grown directly inside or on a matrix, scaffold or device, information shall be provided on the validation of the cell culture process with respect to cell-growth, function and integrity of the combination.

3.3.2.3. Characterisation and control strategy

(a) Relevant information shall be provided on the characterisation of the cell population or cell mixture in terms of identity, purity (e.g. adventitious microbial agents and cellular contaminants), viability, potency, karyology, tumourigenicity and suitability for the intended medicinal use. The genetic stability of the cells shall be demonstrated.

(b) Qualitative and, where possible, quantitative information on product- and process-related impurities, as well as on any material capable of introducing degradation products during production, shall be provided. The extent of the determination of impurities shall be justified.

(c) If certain release tests cannot be performed on the active substance or finished product, but only on key intermediates and/or as in-process testing, this shall be justified.

(d) Where biologically active molecules (such as growth factors, cytokines) are present as components of the cell-based product, their impact and interaction with other components of the active substance shall be characterised.

(e) Where a three-dimensional structure is part of the intended function, the differentiation state, structural and functional organisation of the cells and, where applicable, the extracellular matrix generated shall be part of the characterisation for these cell-based products. Where needed, non-clinical investigations shall complement the physicochemical characterisation.

3.3.2.4. Excipients

For excipient(s) used in cell or tissue-based medicinal products (e.g. the components of the transport medium), the requirements for novel excipients, as laid down in Part I of this Annex, shall apply, unless data exists on the interactions between the cells or tissues and the excipients.

3.3.2.5. Developmental studies

The description of the development program shall address the choice of materials and processes. In particular, the integrity of the cell population as in the final formulation shall be discussed.

3.3.2.6. Reference materials

A reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterised.

3.4. Specific requirements for advanced therapy medicinal products containing devices

3.4.1. *Advanced therapy medicinal product containing devices as referred to in Article 7 of Regulation (EC) No 1394/2007*

A description of the physical characteristics and performance of the product and a description of the product design methods shall be provided.

The interaction and compatibility between genes, cells and/or tissues and the structural components shall be described.

3.4.2. *Combined advanced therapy medicinal products as defined in Article 5(1), point (9)*

For the cellular or tissue part of the combined advanced therapy medicinal product, the specific requirements for somatic cell therapy medicinal products and tissue engineered products set out in section 3.3 shall apply and, in the case of genetically modified cells, the specific requirements for gene therapy medicinal products set out in section 3.2 shall apply.

The medical device or the active implantable medical device may be an integral part of the active substance. Where the medical device or active implantable medical device is combined with the cells at the time of the manufacture or application or administration of the finished products, they shall be considered as an integral part of the finished product.

Information related to the medical device or the active implantable medical device (which is an integral part of the active substance or of the finished product) which is relevant for the evaluation of the combined advanced therapy medicinal product shall be provided. This information shall include:

(a) information on the choice and intended function of the medical device or implantable medical device and demonstration of compatibility of the device with other components of the product;

(b) evidence of conformity of the medical device part or the active implantable device part with the essential requirements laid down in Annex I to Regulation (EU) 2017/745;

(c) where applicable, evidence of compliance of the medical device or implantable medical device with the BSE/TSE requirements laid down in Commission Regulation (EU) No 722/2012[7];

(d) where available, the results of any assessment of the medical device part or the active implantable medical device part by a notified body in accordance with Regulation (EU) 2017/745.

The notified body which has carried out the assessment referred to in point (d) of this section shall make available on request of the competent authority assessing the application, any information related to the results of the assessment in accordance with Regulation (EU) 2017/745. This may include information and documents contained in the conformity assessment application concerned, where necessary for the evaluation of the combined advanced therapy medicinal product as a whole.

[7] Commission Regulation (EU) No 722/2012 of 8 August 2012 concerning particular requirements as regards the requirements laid down in Council Directives 90/385/EEC and 93/42/EEC with respect to active implantable medical devices and medical devices manufactured utilising tissues of animal origin (OJ L 212, 9.8.2012, p. 3, ELI: http://data.europa.eu/eli/reg/2012/722/oj).

4. SPECIFIC REQUIREMENTS REGARDING MODULE 4

4.1. Specific requirements for all advanced therapy medicinal products

The requirements of Part I, Module 4 of this Annex on the pharmacological and toxicological testing of medicinal products may not always be appropriate due to unique and diverse structural and biological properties of advanced therapy medicinal products. The technical requirements in sections 4.1, 4.2 and 4.3 below explain how the requirements in Part I of this Annex apply to advanced therapy medicinal products. Where appropriate and taking into account the specificities of advanced therapy medicinal products, additional requirements have been set.

The rationale for the non-clinical development and the criteria used to choose the relevant species and models (*in vitro* and *in vivo*) shall be discussed and justified in the non-clinical overview. The chosen animal model(s) may include immuno-compromised, knockout, humanised or transgenic animals. The use of homologous models (e.g. mouse cells analysed in mice) or disease mimicking models shall be considered, especially for immunogenicity and immunotoxicity studies.

In addition to the requirements of Part I, the safety, suitability and biocompatibility of all structural components (such as matrices, scaffolds and devices) and any additional substances (such as cellular products, biomolecules, biomaterials, and chemical substances), which are present in the finished product, shall be provided. Their physical, mechanical, chemical and biological properties shall be taken into account.

4.2. Specific requirements for gene therapy medicinal products

In order to determine the extent and type of non-clinical studies necessary to determine the appropriate level of non-clinical safety data, the design and type of the gene therapy medicinal product shall be taken into account.

4.2.1. *Pharmacology*

(a) *In vitro* and *in vivo* studies of actions relating to the proposed therapeutic use (i.e. pharmacodynamic 'proof of concept' studies) shall be provided using models and relevant animal species designed to show that the nucleic acid sequence reaches its intended target (target organ or cells) and provides its intended function (level of expression and functional activity). The duration of the nucleic acid sequence function and the proposed dosing regimen in the clinical studies shall be provided.

(b) Target selectivity: When the gene therapy medicinal product is intended to have a selective or target-restricted functionality, studies to confirm the specificity and duration of functionality and activity in target cells and tissues shall be provided.

4.2.2. *Pharmacokinetics*

(a) Biodistribution studies shall include investigations on persistence, clearance and mobilisation. Biodistribution studies shall additionally address the risk of germline transmission.

(b) Investigations of shedding and risk of transmission to third parties shall be provided with the environmental risk assessment, unless otherwise duly justified in the application on the basis of the type of product concerned.

4.2.3. *Toxicology*

(a) Toxicity of the finished gene therapy medicinal product shall be assessed. In addition, depending on the type of product, individual testing of active substance and excipients shall be taken into consideration, the *in vivo* effect of expressed nucleic acid sequence-related products which are not intended for the physiological function shall be evaluated.

(b) Single-dose toxicity studies may be combined with safety pharmacology and pharmacokinetic studies, e.g. to investigate persistence.

(c) Repeated dose toxicity studies shall be provided when multiple dosing of human subjects is intended. The mode and scheme of administration shall closely reflect the planned clinical dosing. For those cases where single dosing may result in prolonged functionality of the nucleic acid sequence in humans, repeated toxicity studies shall be considered. The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. A justification for the duration shall be provided.

(d) Genotoxicity shall be studied. However, standard genotoxicity studies shall only be conducted when they are necessary for testing a specific impurity or a component of the delivery system.

(e) Carcinogenicity shall be studied. Standard lifetime rodent carcinogenicity studies shall not be required. However, depending on the type of product, the tumourigenic potential shall be evaluated in relevant *in vivo*/*in vitro* models.

(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, unless otherwise duly justified in the application on the basis of the type of product concerned.

(g) *Additional toxicity studies*

– Integration studies: integration studies shall be provided for any gene therapy medicinal product, unless the lack of these studies is scientifically justified, e.g. because nucleic acid sequences will not enter into the cell nucleus. For gene therapy medicinal products not expected to be capable of integration, integration studies shall be performed, if biodistribution data indicate a risk for germline transmission.

– Immunogenicity and immunotoxicity: potential immunogenic and immunotoxic effects shall be studied.

4.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products

4.3.1. *Pharmacology*

(a) The primary pharmacological studies shall be adequate to demonstrate the proof of concept. The interaction of the cell-based products with the surrounding tissue shall be studied.

(b) The amount of product needed to achieve the desired effect/the effective dose, and, depending on the type of product, the frequency of dosing shall be determined.

(c) Secondary pharmacological studies shall be taken into account to evaluate potential physiological effects that are not related to the desired therapeutic effect of the somatic cell therapy medicinal product, of the tissue engineered product or of additional substances, as biologically active molecules besides the protein(s) of interest might be secreted or the protein(s) of interest could have unwanted target sites.

4.3.2. *Pharmacokinetics*

(a) Conventional pharmacokinetic studies to investigate absorption, distribution, metabolism and excretion shall not be required. However, parameters such as viability, longevity, distribution, growth, differentiation and migration shall be investigated, unless otherwise duly justified in the application on the basis of the type of product concerned.

(b) For somatic cell therapy medicinal products and tissue engineered products, producing systemically active biomolecules, the distribution, duration and amount of expression of these molecules shall be studied.

4.3.3. *Toxicology*

(a) The toxicity of the finished product shall be assessed. Individual testing of active substance(s), excipients, additional substances and any process-related impurities shall be taken into consideration.

(b) The duration of observations may be longer than in standard toxicity studies and the anticipated lifespan of the medicinal product, together with its pharmacodynamic and pharmacokinetic profile, shall be taken into consideration. A justification of the duration shall be provided.

(c) Conventional carcinogenicity and genotoxicity studies shall not be required, except with regard to the tumourigenic potential of the product.

(d) Potential immunogenic and immunotoxic effects shall be studied.

(e) In the case of cell-based products containing animal cells, the associated specific safety concerns such as transmission to humans of xenogeneic pathogens shall be addressed.

5. SPECIFIC REQUIREMENTS REGARDING MODULE 5

5.1. Specific requirements for all advanced therapy medicinal products

5.1.1. The specific requirements in this section of Part IV are additional requirements to those set in Module 5 in Part I of this Annex.

5.1.2. Where the clinical application of advanced therapy medicinal products requires specific concomitant therapy and involve surgical procedures, the therapeutic procedure as a whole shall be investigated and described. Information on the standardisation and optimisation of those procedures during clinical development shall be provided.

Where medical devices used during the surgical procedures for application, implantation or administration of the advanced therapy medicinal product may have an impact on the efficacy or safety of the advanced therapy product, information on these devices shall be provided.

Specific expertise required to carry out the application, implantation, administration or follow-up activities shall be defined. Where necessary, the training plan of health care professionals on the use, application, implantation or administration procedures of these products shall be provided.

5.1.3. Given that, due to the nature of advanced therapy medicinal products, their manufacturing process may change during clinical development, additional studies to demonstrate comparability may be required.

5.1.4. During clinical development, risks arising from potential infectious agents or the use of material derived from animal sources and measures taken to reduce such risk shall be addressed.

5.1.5. Dose selection and schedule of use shall be defined by dose-finding studies.

5.1.6. The efficacy of the proposed indications shall be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use. In certain clinical conditions, evidence of long-term efficacy may be required. The strategy to evaluate long-term efficacy shall be provided.

5.1.7. A strategy for the long-term follow-up of safety and efficacy shall be included in the risk management plan.

5.1.8. For combined advanced therapy medicinal products, the safety and efficacy studies shall be designed for and performed on the combined product as a whole.

5.2. Specific requirements for gene therapy medicinal products

5.2.1. *Human pharmacokinetic studies*

Human pharmacokinetic studies shall include the following aspects:

(a) shedding studies to address the excretion of the gene therapy medicinal products;

(b) biodistribution studies;

(c) pharmacokinetic studies of the medicinal product and the gene expression moieties (e.g. expressed proteins or genomic signatures).

5.2.2. *Human pharmacodynamic studies*

Human pharmacodynamic studies shall address the expression and function of the nucleic acid sequence following administration of the gene therapy medicinal product.

5.2.3. *Safety studies*

Safety studies shall address the following aspects:

(a) emergence of replication competent vector;

(b) emergence of new strains;

(c) reassortment of existing genomic sequences;

(d) neoplastic proliferation due to insertional mutagenicity.

5.3. Specific requirements for somatic cell therapy medicinal products

5.3.1 *Somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s)*

For somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s), the pharmacokinetic profile (in particular distribution, duration and amount of expression) of those molecules shall be addressed, if feasible.

5.3.2. *Biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components*

The biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components shall be addressed during the clinical development.

5.3.3. *Safety studies*

Safety studies shall address the following aspects:

(a) distribution and engrafting following administration;

(b) ectopic engraftment;

(c) oncogenic transformation and cell/tissue lineage fidelity.

5.4. Specific requirements for tissue engineered products

5.4.1 *Pharmacokinetic studies*

Where conventional pharmacokinetic studies are not relevant for tissue engineered products, the biodistribution, persistence and degradation of the tissue engineered product components shall be addressed during the clinical development.

5.4.2. *Pharmacodynamic studies*

Pharmacodynamic studies shall be designed and tailored to the specificities of tissue engineered products. The evidence for the ‘proof of concept’ and the kinetics of the product to obtain the intended regeneration, repairing or replacement shall be provided. Suitable pharmacodynamic markers, related to the intended function(s) and structure shall be taken into account.

5.4.3. *Safety studies*

Section 5.3.3 shall apply.

ANNEX III

Conditions of qualification of a qualified person

1. The qualified person referred to in Article 155 shall possess evidence of formal qualifications awarded on completion of a university course of study, or a course recognised as equivalent by the Member State concerned, extending over a period of at least four years of theoretical and practical study, in one or more of the following scientific disciplines: pharmacy, medicine, veterinary medicine, chemistry, pharmaceutical chemistry and technology, biology, biomedical engineering and biotechnology and chemical engineering.

However, the minimum duration of the university course or the course recognised as equivalent by the Member State concerned may be three and a half years where it is followed by a period of theoretical and practical training of at least one year, that includes a training period of at least six months in a pharmacy open to the public, corroborated by an examination at university level.

Where two university courses or two courses recognised as equivalent by the Member State co-exist in a Member State and where the duration of one of those courses is four years and the other three years, the three-year course or its recognised equivalent shall be considered to fulfil the condition of duration referred to in the second subparagraph in so far as evidence of formal qualifications awarded on completion of both courses are recognised as equivalent by the Member State in question.

The course shall include theoretical and practical study bearing upon at least the following basic subjects:

(a) Physics

(b) General and inorganic Chemistry

(c) Organic chemistry

(d) Analytical chemistry

(e) Pharmaceutical chemistry, including analysis of medicinal products

(f) Biochemistry

(g) Physiology

(h) Microbiology

(i) Pharmacology

(j) Pharmaceutical technology

(k) Toxicology.

Studies in these subjects shall be so balanced as to enable the person concerned to fulfil the obligations specified in Article 157.

In so far as a person does not possess evidence of formal qualifications referred to in the first subparagraph or otherwise does not fulfil the criteria laid down in this paragraph, the competent authority of the Member State shall ensure that the person concerned provides evidence of adequate knowledge of the subjects involved.

2. The qualified person shall have acquired at least two years full-time practical experience or an equivalent amount of experience acquired over a proportionally longer period of time, in one or more undertakings or entities not engaged in an economic activity that are authorised manufacturers, during which time the qualified person shall have obtained sufficient knowledge of manufacture, testing, supply chains, good manufacturing practice and pharmaceutical quality systems as well as regulatory processes and dossier content to be able to ensure the quality of medicinal products. Where the duration of the university course or the course recognised as equivalent by the Member State concerned as referred to in paragraph 1 is at least five years, the competent authority of the Member State may reduce the period of practical experience by one year.

3. Where, from the time of the application of Second Council Directive 75/319/EEC[1], a person has been engaged in a Member State in the activities of a qualified person as referred to in Article 155 without complying with this Annex, that person shall be eligible to continue to engage in those activities within the Union.

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1 Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products (OJ L 147, 9.6.1975, p. 13, ELI: http://data.europa.eu/eli/dir/1975/319/oj).

4. Where the holder of a diploma, certificate or other evidence of formal qualifications awarded on completion of a university course, or a course recognised as equivalent by the Member State concerned, in a scientific discipline allowing them to engage in the activities of the qualified person referred to in Article 155 in accordance with the laws of that Member State, began their course prior to 21 May 1975, that person may be considered as being qualified to carry out the duties of a qualified person as referred to in Article 155 in that Member State provided that that person has engaged in the following activities for at least two years before 21 May 1985 in one or more undertakings or not-for-profit entities authorised to manufacture: production supervision or qualitative and quantitative analysis of active substances, and the necessary testing and checking under the direct authority of a qualified person as referred to in Article 155 to ensure the quality of the medicinal products.

ANNEX IV

Labelling particulars

The following particulars shall appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging:

(a) the name of the medicinal product, including in Braille, followed by its strength, if appropriate, including in Braille and by its pharmaceutical form, if appropriate, including in Braille, and, if appropriate, whether it is intended for babies, children or adults;

(b) where the medicinal product contains up to three active substances, the international non-proprietary name (INN), unless it is already part of the name of the medicinal product, or, if there is no INN, the common name;

(c) a statement of the active substances expressed qualitatively and quantitatively per dose or unit or according to the form of administration for a given volume or weight, using their common names;

(d) the pharmaceutical form and the contents by weight, by volume or by number of doses of the medicinal product;

(e) a list of those excipients known to have a recognised action or effect and included in the detailed guidance published pursuant to Article 80;

(f) the method of administration and, if necessary, the route of administration. Space shall be provided for the prescribed dose to be indicated;

(g) a special warning that the medicinal product must be stored out of the reach and sight of children;

(h) a special warning, if necessary for the medicinal product;

(i) the expiry date in clear terms (month/year);

(j) special storage precautions, if any;

(k) specific precautions relating to the disposal of unused medicinal products or waste derived from medicinal products as well as reference to any appropriate collection system in place;

(l) the name and address of the marketing authorisation holder and, where applicable, the name of the marketing authorisation holder representative;

(m) the marketing authorisation number;

(n) the manufacturer’s batch number;

(o) in the case of medicinal products not subject to medical prescription, instructions for use;

(p) for medicinal products other than radiopharmaceuticals referred to in Article 70(1), safety features enabling manufacturers, wholesale distributors, pharmacists and other natural or legal persons authorised or entitled to supply medicinal products to the public and the competent authorities of the Member States or the Agency, as applicable, to:

(i) verify the authenticity of the medicinal product, and

(ii) identify individual packs,

as well as a device allowing verification of whether the outer packaging has been tampered with.

ANNEX V

Contents of summary product characteristics

The summary of product characteristics referred to in Article 65 shall contain, in the order indicated below, the following information:

(1) name of the medicinal product followed by the strength and the pharmaceutical form.

(2) qualitative and quantitative composition in terms of the active substances and of the excipient, knowledge of which is essential for proper administration of the medicinal product. The usual common name or chemical description shall be used.

(3) pharmaceutical form.

(4) clinical particulars:

4.1 therapeutic indications,

4.2 posology and method of administration for adults and, where necessary, for children,

4.3 contra-indications,

4.4 special warnings and precautions for use and, in the case of immunological medicinal products, any special precautions to be taken by persons handling such medicinal products and administering them to patients, together with any precautions to be taken by the patient,

4.5 interaction with other medicinal products and other forms of interactions,

4.6 use during pregnancy, breastfeeding, during periods when people are trying to conceive, and information on effects on fertility,

4.7 effects on ability to drive and to use machines,

4.8 undesirable effects including standardised text expressly asking healthcare professionals to report any suspected adverse reaction through the national reporting system or by other means and specifying the different ways of reporting available (electronic reporting, postal address or others) in accordance with Article 110(1), second subparagraph,

4.9 overdose (symptoms, emergency procedures, antidotes).

(5) pharmacological properties:

5.1 pharmacodynamic properties,

5.2 pharmacokinetic properties,

5.3 non-clinical safety data.

(6) pharmaceutical particulars:

6.1 list of excipients,

6.2 major incompatibilities,

6.3 shelf life and, when necessary, shelf life after reconstitution or dilution of the medicinal product or when the immediate packaging is opened for the first time,

6.4 precautions for storage,

6.5 nature and contents of container,

6.6 precautions to be taken for the disposal of a medicinal product or waste materials derived from such medicinal product, if appropriate, and, in the case of antimicrobials, a warning that inappropriate disposal of the medicinal product contributes to antimicrobial resistance.

(7) name and address of the marketing authorisation holder.

(8) marketing authorisation numbers.

(9) date of the first marketing authorisation or of the renewal of the marketing authorisation.

(10) date of revision of the text.

(11) for radiopharmaceuticals, full details of internal radiation dosimetry.

(12) for radiopharmaceuticals, additional detailed instructions for extemporaneous preparation and quality control of such preparation and, where appropriate, maximum storage time during which any intermediate preparation such as an eluate or the ready-to-use pharmaceutical will conform with its specifications.

ANNEX VI

Contents of package leaflet

The package leaflet referred to in Article 67 shall contain, in the order indicated below, the following information:

(1) for the identification of the medicinal product:

(a) the name of the medicinal product followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults. The common name shall be included where the medicinal product contains only one active substance and if its name is an invented name;

(b) the pharmaco-therapeutic group or type of activity in terms easily comprehensible for the patient;

(2) the therapeutic indications;

(3) a list of information that is necessary before the medicinal product is taken:

(a) contra-indications;

(b) appropriate precautions for use;

(c) forms of interaction with other medicinal products and other forms of interaction (e.g. alcohol, tobacco, food and herbal products) that may affect the action of the medicinal product;

(d) special warnings;

(4) the necessary and usual instructions for proper use, and in particular:

(a) the dose and posology,

(b) the method including any necessary step for preparation and use of any required device for measurement or delivery and, if necessary, route of administration;

(c) the frequency of administration, specifying if necessary the appropriate time at which the medicinal product may or must be administered;

and, as appropriate, depending on the nature of the medicinal product:

(d) the duration of treatment, where it should be limited;

(e) the action to be taken in the case of an overdose (such as symptoms, emergency procedures);

(f) what to do when one or more doses have not been taken;

(g) indication, if necessary, of the risk of withdrawal effects;

(h) a specific recommendation to consult the doctor or the pharmacist, as appropriate, for any clarification on the use of the medicinal product;

(5) a description of adverse reactions that might occur under normal use of the medicinal product and, if necessary, the action to be taken in such a case, including standardised text expressly asking patients to report any suspected adverse reaction to their doctor, pharmacist, healthcare professional or directly through the national reporting system, and specifying the different ways of reporting available (electronic reporting, postal address or others) in accordance with Article 110(1), second subparagraph;

(6) references to the following:

(a) the expiry date indicated on the label, with a warning against using the medicinal product after that date;

(b) where appropriate, storage precautions;

(c) if necessary, a warning concerning certain visible signs of deterioration;

(d) the full qualitative composition (in active substances and excipients) and the quantitative composition in active substances, using common names, for each presentation of the medicinal product;

(e) for each presentation of the medicinal product, the pharmaceutical form and content in weight, volume or units of dosage;

(f) information on where the package leaflet is available in formats accessible for persons with disabilities;

(g) the name, address and e-mail address of the marketing authorisation holder and, where applicable, the name of the marketing authorisation holder representative in the Member States;

(h) the name and address of the manufacturer.

(7) the date on which the package leaflet was last revised.

(8) For antimicrobials, a section that contains the global antimicrobial resistance symbol, specific information about the medicinal product concerned and information on antimicrobial resistance and on the importance of appropriate use and disposal of antimicrobials referred to in Article 72(2).

The list set out in point (3) shall:

(a) take into account the particular condition of certain categories of users (children, pregnant or breastfeeding women, elderly, persons with specific pathological conditions and persons with disabilities);

(b) mention, if appropriate, possible effects on the ability to drive vehicles or to use machines;

(c) list those excipients the knowledge of which is important for the safe and effective use of the medicinal product.

ANNEX VII

Areas for adapted frameworks referred to in Article 31

Phage-containing medicinal products, in cases where the medicinal product has a variable composition depending on the specific clinical context.

ANNEX VIII

Correlation table

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