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CONTRIBUTION

From:	General Secretariat of the Council
To:	Working Party on Pharmaceuticals and Medical Devices (Attachés) Pharmaceutical package
Subject:	Pharma package - Comments from the delegations

Delegations will find enclosed comments from delegations on Reading package 1 (general and authorisations) and Reading package 6 (procedures for national marketing authorisations).

COMMENTS FROM THE DELEGATIONS

On Reading package 1 (general and authorisations) and Reading package 6 (procedures for national marketing authorisations)

AUSTRIA

Reading Package 1

Directive

- AT General Remark:

It should be assessed whether the Directive contains provisions that should be part of the Regulation. Provisions that transfer powers over individual to the Commission should be regulated in the Regulation, e. g. Art. 195 and following:

  - Art. 195 para. 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 or that it lacks therapeutic efficacy, or 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."
  - Further examples in the next paragraphs (of Art. 195) that include the following phrase: **"in the case of centralised marketing authorisation, the Commission" …**

- AT Art. 25ff: We want to see **master files related to platform technologies** to be included, because this will simplify the authorization process

- AT: Annex 1:

Possibility to authorise generic products via national procedure for substances authorised after 2004 must be kept

It is of high importance to replace 20 May 2004 by "the date of entry into force of this Regulation". Not allowing generic products to be authorized via national procedures (except for old products) anymore might lead to less authorisations and a higher risk for shortages. It is questionable whether the agency can handle the immense workload as the vast majority of generic applications are currently managed and assessed by the national competent authorities.

Proposal AT:

*3. Medicinal products for human use containing a **new** active substance which on ~~20 May 2004~~ **the date of entry into force of this Regulation**, was not authorised in the Union, excluding allergen products or herbal medicinal products, which shall in any case not be authorised by the Union.*

Regulation

- AT Rec 73, Art. 6: Restriction to quality master files is to narrow, it would be desirable to include master files related to platform technologies too. This could lead to simplification of the authorization procedure.

- AT Art. 7 para. 3:

This provision does not appear to be consistent with the recitals and the rest of the provision. In particular, the added exclusion of any medicinal products for human use containing or consiting of GMOs from the whole Directive 2009/41/EC is not consistent with para 4 (which only stipulates a partial exemption) and para 5 below.

Furthermore, this addition raises the question whether any activity related to an (authorised or non authorised) medicinal product, including e.g. its manufacturing, beginning from starting materials, should be excempt or only certain activities related to an already manufactured/finished medicinal product.

- AT Art. 26 para. 1:

We still have strong reservations about the second sentence of this provision and propose its deletion for the following reasons: The marketing authorisation is only the prerequesite for the placing on the market of medicinal products (see also Article 5 of the revised Directive), however, not for the application/use of medicinal products. Therefore, the application of medicinal products for other therapeutic uses than for which they are authorised (off label use) is not restricted by the provisions regarding marketing authorisation Against this background, there is no point in stipulating an allowance for the making available of authorised medicinal products for other/new therapeutic uses only under the conditions of compassionate use; such medicinal products may already be placed on the marked and used for (off label) patient care based on their existing marketing authorisation. To this effect, off label use of authorised medicinal products is considered permissible in Austria in accordance with the general rules of patient care and professional law of physicians – the fulfilment of the conditions for compassionate use are not a prerequisite for the treatment of patients in such cases. The second sentence of Article 26 indicates otherwise. As we cannot agree with such an understanding, we propose a corresponding amendment. Furthermore, the second sentence is not consistent with the definition of compassionate use itself in para 2: This definition applies only if a disease cannot be treated satisfactorily by an “authorised medicinal product”. Cases in which an authorised medicinal product shall be used for a new therapeutic indication (second sentence of para 1) could therefore never fulfill the definition criteria of “compassionate use”. Also against this background, we propose the deletion of the second sentence of para 1.

Reading Package 6

- AT Art. 34 para. 6 and Art. 36 para. 6:

The wording of these provisions gives the impression that the Member States must in any case approve the assessment report etc. within 90 days. For greater clarity, we therefore suggest that the possibility of divergent positions (Article 38 et seq). should already be mentioned at this point.

- AT Art. 46 para. 4:

It should be considered whether the competent authorities should – also upon renewal – have the option to restrict the duration of validity (in parallel to para 1).

BELGIUM

Just to confirm that we support the FR comments on art. 22.3 (ERA)

Article 22.3 (ERA):
A combined reading of recital 69 and paragraph 3 of article 22 leads the French authorities to propose reverting to the Commission's initial version.
Paragraph 3 is not linked to paragraph 1, which requires an environmental risk assessment to be carried out by the manufacturer and the competent national authorities or the EMA. Paragraph 3 concerns the transmission by industry of measures to reduce emissions into the air, water or soil of pollutants identified in sectoral directives. No assessment is required for these pollutants. The first part of the sentence should therefore be deleted.
As a reminder, the original wording was as follows:
3. The applicant shall also include in the ERA risk mitigation measures to avoid or where it is not possible, limit emissions to air, water and soil of pollutants listed in Directive 2000/60/EC, Directive 2006/118/EC, Directive 2008/105/EC and Directive 2010/75/EU. The applicant shall provide detailed explanation that the proposed mitigation measures are appropriate and sufficient to address the identified risks to the environment.

BULGARIA

We support the Presidency proposals, as last circulated.

I take the occasion to reiterate our negative reserve on massive redrafting suggestions in these clusters last-minute, in particular on ERA-related texts.

CROATIA

My capital has analyzed the Dutch proposals on ERA provisions and they have asked me to reaffirm our position in support of the current Presidency proposal that was discussed at the last WP meeting on 15 April.

Like our BG colleagues, we will not be able to support any changes going in the different direction from the latest Presidency text, which is how we interpret the NL proposals.

CZECH REPUBLIC

Directive
Art. 34 para. 3a
CZ is still of the opinion that it should be clarified that if the applicant does not provide requested information in the determined period of time the MAA shall be considered withdrawn in all CMS, not only RMS. Therefore, we propose to amend the last sentence in this para. Please see the changes in wording proposed.

If the applicant fails for provide the mission information and documentation within the time limit set, the application shall be considered to have been withdrawn ***in all Member States in which it was submitted.***

FINLAND

Reading package 1
Chapter 2
Application requirements for national and centralized marketing authorisations
Article 6. para 3a

Justification:
Primarily, we propose that this section should be completely removed. The proposal could lead to a large number of products being released on the market just before the marketing authorisation is withdrawn, in order to avoid, among other things, the annual fees of the marketing authorisation. This could also lead to products being on the market for a long time after the marketing authorisation has been withdrawn. Additionally, due to system-related reasons, products cannot even be sold after the marketing authorisation has been withdrawn.

Second option, it should be stipulated that the sale of products is permitted for a specific period, for example, six months after the marketing authorisation withdrawal, during which the marketing authorisation holder's obligations would remain.

FI proposal:
Where a marketing authorisation is withdrawn, but medicinal product previously placed on the market under that marketing authorisation remains to be made available on the market, all relevant obligations and post-marketing provisions of this Directive and of [revised Regulation 726/2004/EC] shall continue to apply as appropriate until such time as all remaining stock of the medicinal product has expired. ***Medicinal products may remain on the market for six months after the withdrawal of the marketing authorisation***.

FRANCE

Article 22.3 (ERA):

A combined reading of recital 69 and paragraph 3 of article 22 leads the French authorities to propose reverting to the Commission's initial version.

Paragraph 3 is not linked to paragraph 1, which requires an environmental risk assessment to be carried out by the manufacturer and the competent national authorities or the EMA. Paragraph 3 concerns the transmission by industry of measures to reduce emissions into the air, water or soil of pollutants identified in sectoral directives. No assessment is required for these pollutants. The first part of the sentence should therefore be deleted.

As a reminder, the original wording was as follows:

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

On the definition of a reference medicinal product (12) :

The French authorities would like to add articles 13 or 14 to the definition of a reference drug. Indeed, the reference drug may have been authorized on the basis of a bibliographic dossier or informed consent, both of which are considered complete dossiers.

The following amendment is proposed:

(12) reference medicinal product: “means a medicinal product that is or has been authorised by a Member State or by the Commission in the Union under Article 5, in accordance with Article 6, **13 or 14”.**

Article 40D (MA harmonization procedure) :

The French authorities wish to complete this article, as a procedure for harmonizing the wording of marketing authorizations can be carried out by the CMDh (Coordination Group for the Decentralized Procedure and the Mutual Recognition Procedure). This is a welcome possibility. However, it is necessary to provide for the modalities and, at the very least, the finalization and binding nature of the CMDh opinion, or the fact that the majority position of the CMDh (in the event of non-consensus) must be forwarded to the Commission for decision. In the absence of such provisions, registrants will not be obliged to submit variations aimed at adopting the harmonized wording adopted.

Consequently, it is proposed to add, at the end of the article, how the opinion of the coordination group (CMDh) will be made opposable and therefore applicable to all laboratories concerned.

The following amendment is proposed:

“If 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 Commission shall apply the procedure laid down in Article 42”.

GERMANY

I. General comments

DE can in general support the clusters Reading Package 1 (general and authorisations) and 6 (procedures for national marketing authorisations) included in document st16051/24 but has some important

comments and amendments that are of technical nature (II), especially regarding the requirements for environmental risk assessments (see also III).

II. Detailed comments

Article 9 Directive – Applications concerning generic medicinal products

- Article 9 paragraph 2 (doc. 16051/24, page 61):
  2. For the purpose of demonstrating the equivalence as referred to in paragraph 1, the applicant shall submit to the competent authorities equivalence studies, or a **scientific** justification as to why such studies **are not needed** ~~were not performed~~, and demonstrate that the generic medicinal product meets the relevant criteria set out in the appropriate detailed guidelines.
- Annex II (page 48):
  an evaluation of the bio-equivalence studies or a **scientific** justification why studies **are not needed** ~~were not performed~~ with respect to the guideline on 'Investigation of Bio-availability and Bio-equivalence';
- *Rationale:* Even if we prefer to replace „equivalence" with „bioequivalence" we recognise that a large majority of MS support the COM's initial proposal. A specification in the legal text depending on the pharmaceutical form of a medicinal product (e.g. bioequivalence for systemic products and equivalence for topical products) did not find a majority either. Based on Annex II of the revised directive stated that for generics the application shall contain (…) data showing bio-availability and bio-equivalence with the original medicinal product and that for these prodcuts the non-clinical/clinical overviews/summaries shall particularly focus on an evaluation of the bio-equivalence studies or a justification why studies were not performed with respect to the guideline on ‚Investigation of Bioavailability and Bio-equivalence', we can accept the current compromise text *in the understanding that the use of the term "equivalence" in Article 9 is an overall term which is further specified in Annex II for different kinds of medicinal products. Due to that specification, bio-equivalence is and must be the criterion for generics, as before*. However, for clarification, we ask for an adjustment to para 2 and Annex II. The justifications why a (bio)equivalence study is not needed should be science based.

Article 16 Directive – Radiopharmaceuticals

- Article 16 paragraph 1 (doc. 16051/24, page 65)
  1. A marketing authorisation shall be required for radionuclide generators, kits **for radiopharmaceutical preparation**, and radionuclide precursors , unless theyare used as starting material, active substance or intermediate of radiopharmaceuticals covered by a marketing authorisation under Article 5(1). **Member States may, in justified cases, regulate substance-related exemptions from the authorization requirement for radionuclide precursors for diagnostic radioactive medicinal products, if this is necessary to secure an adequate supply of radionuclides throughout the facilities for nuclear medicine and if the safety and quality profile for the radionuclide precursor is established and assured.**

- *Rationale:* With regard to the supply situation and in order not to restrict potential future developments it would also be conceivable to design an exemption from the authorisation requirement for radionuclide precursors in the responsibility of the Member States. In detail we are aware of problems with the availability of diagnostic radioactive medicinal products labelled with the radionuclide fluorine-18, which are intended for positron emission tomography (PET). It is about a long-established product in terms of its production and quality and there is an increasing demand for(18F)fluoride solution for radiolabelling. The solution has to be manufactured at a cyclotron and due to its very short physical half-life (109,8 minutes) it cannot be produced in advance. A delivery of (18F)fluoride solution for radiolabelling from a nuclear medicine center with a cyclotron to a neighbouring nuclear medicine center without a cyclotron is possible if the distance between the two centers is not too long but in these cases an marketing authorisation is required. There are no concerns to exempt (18F)fluoride solution for radiolabelling from the approval requirement due to the established and reliable manufacturing process at the cyclotron as well as the established quality standards are described in the pharmacopoeia.

Article 27 Directive – Excipients

- Para 8 *new*: Paragraph 6 shall not apply to food-producig-animals as defined in Article 4(38) of Regulation (EU) 2019/6 of the European Parliament and of the Council.
- *Rationale*: According to para 6, a colour that has been removed from the Union list of authorised food additives can still be used as a colour in medicinal products until otherwise decided by COM. Although we understand the fundamental intention to separate human and veterinary medicinal products, veterinary medicinal products will be explicitly included in para. 7. Against this background, it appears necessary to exclude food-producing animals from the regulation in para 6. Colours should not be used in veterinary medicinal products used in food-producing animals.

Article 6 Regulation – Centralised marketing authorisation

- Article 6 paragraph 2 (doc. 16051/24, page 82+83)

  2. For medicinal products that ~~are likely to offer an exceptional therapeutic advancement in the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Union,~~ **are intended to be used in relation to potential or declared public health emergency** the Agency may, following the advice of the Committee for Medicinal Products for Human Use regarding the maturity of the data related to the development, offer to the applicant a phased review of complete data packages for individual modules of particulars and documentation as referred to in paragraph 1.

  The Agency may at any stage suspend or cancel the phased review, where the Committee for Medicinal Products for Human Use considers that the submitted data are not of sufficient maturity or where it is considered that the medicinal product **cannot be used in relation to potential or**

declared public health emergency~~no longer fulfils an exceptional therapeutic advancement. The Agency shall inform the applicant accordingly~~.

- *Rationale: The option of a phased review should be mainted in addition to a TEMA. We prefer the wording from the first compromise text (doc. 11863/24) with the limitation of the phased review to medicinal products that are intended to be used in relation to potential or declared public health emergency.*

Article 12 Regulation – Committee Opinion

- Article 12 paragraph 1 lit. ii (doc. 16051/24, page 90) – *For our proposal on the ERA requirement for marketing authorisation application, see III.*

Article 15 Regulation – Refusal of a centralised marketing authorisation

For our proposal on the ERA requirement for marketing authorisation application, see III.

Article 19 Regulation – Conditional marketing authorisation

- Article 19 paragraph 3 (doc. 16051/24, page 103)

  3. Conditional marketing authorisations or a new conditional therapeutic indication granted pursuant to this Article shall be subject to specific obligations. Those specific obligations and, where appropriate, the time limit for compliance shall be specified in the conditions to the marketing authorisation. Those specific obligations shall be reviewed annually by the Agency for the first three years after granting the authorisation and every two years thereafter.
- *Rationale:* The last sentence of this paragraph should be maintained. This approach seems appropriate in the light of the COM's explanations and reduces the burden on the authorities.

Article 20 Regulation - Imposed post-authorisation studies

- Article 20 paragraph 1 lit. c (doc. 16051/24 page 104)

  c) conducts a post-authorisation environmental risk assessment study, collection of monitoring data or information on use, if there are concerns about ~~to further investigate~~ the risks to the environment or public health, including antimicrobial resistance, due to ~~the release of the medicinal product in the environment, if new concerns emerge on the~~ an authorised medicinal product, or other medicinal products containing the same active substance.

- *Rationale:* Post-authorisation environmental risk assessment studies were mentioned in different articles in the revised directive (article 44 para 1 lit. h and article 87 para 1 lit. c) and the revised regulation (article 12 para 4 lit. j and article 20 para 1 lit. c). The wording between the directive and regulation should be coherent.

Article 26 Regulation – Medicinal products for compassionate use

- Article 26 para 8 (doc. 16051/24 page 108)

  8. Where a compassionate use programme has been set up in accordance with paragraphs 1 and 5, the applicant shall ensure that patients taking part also have access to the new medicinal product **if**

~~necessary until the medicine is made available on the market of the Member State concerned~~**.** **until the end of the** ~~in the course of their treatment, including the case~~ **when the compassionate use progamme has ended.** ~~during the period between authorisation and placing on the market.~~ during the period between authorisation and placing on the market.

- *Rationale*: DE prefers COM´s proposal for the sake of legal clarity.

Article 36 Directive – Mutual recognition procedure for national marketing authorisations

- Article 36 paragraph 4 (doc. 16051/24, page 368)
  4. The applicant shall inform the competent authorities of all Member States of its application at the time of submission **referred to in paragraph 1. If necessary to meet the needs of patients in that Member State,** ~~T~~the competent authority of a Member State may request for justified public health reasons to enter the procedure and shall inform the applicant and the competent authority of the reference Member State for the mutual recognition procedure of its request within 30 days from the date of submission ~~**validation**~~ of the application. The applicant shall provide the competent authorities of those Member States entering the procedure with the application without undue delay. **The Member State that requests to enter the decentralised procedure under this paragraph shall be considered as Member State concerned.**
- *Rationale:* For reasons of coherence to Article 34 paragraph 3 the last sentence should be added.

Article 41 Directive – Scientific evaluation by the Committee for Medicinal Products for Human Use in a referral procedure

- Art. 41 Directive para 4 (doc. 16051 page 375)
- 4. The Agency shall without undue delay inform the applicant or the marketing authorisation holder where the opinion of the Committee for Medicinal Products for Human Use provides that:
  (c) the 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 and enviromental issues;

- *Rationale*: Risks from pharmaceutical residues in the environment, which can have adverse effects on public health, are also likely to pose serious risks in individual cases.

Article 44 Directive – National marketing authorisation subject to conditions

- Article 44 paragraph 1 lit. ga (doc. 16051/24, page 381), *see III.*

Article 47 Directive – Refusal of a national marketing authorisation

For our proposal on the ERA requirement for marketing authorisation application, see III.

Recital 70 Directive

For our proposal on the ERA requirement for marketing authorisation application, see III.

III. Proposal on ERA requirement for marketing authorisation applications

Directive

(70) Marketing authorisation applications for medicinal products in the Union should include an Environmental Risk Assessment (ERA) and **if the ERA identifies a risk to the environment,** risk mitigation measures. If the applicant fails to submit a complete or sufficiently substantiated environmental risk assessment or they do not propose risk mitigation measures to sufficiently address the risks identified in the environmental risk assessment, the marketing authorisation should be refused. **However, in exceptional cases, the applicant can justify that deficiencies can be resolved post authorisation.** ~~**unless the necessary information can be obtained through post-authorisation studies or appropriate risk mitigating measures can be implemented as a condition to marketing authorisation**~~. The ERA should be updated when new data or knowledge about relevant risks become available. **The environmental risk of a medicinal product is not part of the benefit risk balance of a medicinal product.**

Article 44 - National marketing authorisation subject to conditions

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

(…)

(ga) in case of Article 47 paragraph 1 point (d) when deficiencies have been declared and adequately justified, ~~**the environmental risk assessment suffering from deficiencies at the time of application, or if the risk identified in the environmental risk assessment has not been sufficiently addressed by the applicant,**~~ **to address the deficiencies within a reasonable time set by the competent authority** ~~**an agreed timeframe**~~ **and if required to implement appropriate risk mitigation measures;**

Article 47 - Refusal of a national marketing authorisation

1. The national marketing authorisation shall be refused if, after verification of the particulars and documentations referred to in Article 6 and subject to the specific requirements laid down in Articles 9 to 14, the view is taken that:

(...)

(d) ~~**the data for**~~ the environmental risk assessment **is incomplete or insufficiently substantiated by the applicant or if the risks identified in the environmental risk assessment have not been sufficiently addressed by the applicant** ~~**submitted by the applicant suffers from major deficiencies, unless post-authorisation environmental risk assessment studies can be requested or the identified risks can be mitigated with appropriate risk mitigation measures, it is considered, taking into account the benefit of the immediate availability of the medicinal product concerned , that those deficiencies shall be addressed with post-authorisation environmental risk assessment studies risks can be mitigated under a post authorisation obligation referred to in Article 44 (1) ga);**~~ ~~is incomplete or insufficiently substantiated by the applicant or if the risks identified in the environmental risk assessment have not been sufficiently addressed by the applicant;~~ **unless the applicant has declared and adequately justified that the deficiencies that exist at the time of application can be resolved post-authorisation under an obligation referred to in Article 44 (1)(ga);**

Regulation

Article 12- Committee Opinion

(…)

4. If an opinion is favourable to the granting of the relevant marketing authorisation, the following**s** ~~documents~~ shall be annexed to the opinion:

(…)

(ii) in the case of Article 15 paragraph 1 point (d) when deficiencies have been declared and adequately justified, details on any obligation to address the deficiencies within a reasonable time set by the Agency and if required to implement appropriate risk mitigation measures;

Article 15 - Refusal of a centralised marketing authorisation

1. The marketing authorisation shall be refused if, after verification of the particulars and documentation submitted in accordance with Article 6, the view is taken that:

(…)

(d) the environmental risk assessment is incomplete or insufficiently substantiated by the applicant or if the risks identified in the environmental risk assessment have not been sufficiently addressed by the applicant**, unless ~~a post-authorisation environmental risk assessment studies can be requested or the identified risks can be mitigated with appropriate risk mitigation measures~~ the applicant has declared and adequately justified that the deficiencies that exist at the time of application can be resolved post-authorisation under the obligation referred to in Article 12 (4)(ii)**~~-~~;

The default should be that at the time of application the ERA is complete, unless valid reasons exist to obtain missing data post-authorisation. The formulation in the proposal suggests a reversed hierarchy, putting the burden of proof on the competent authorities to justify that ERA data is needed before authorisation because of unacceptable risks.

Our text proposal is aimed at a) preventing the hierarchy is reversed from pre- to post-authorisation and thereby putting the burden of proof on the competent authorities, b) safeguarding that deficiences are resolved post authorisation and c) consistency between Directive and Regulation.

GREECE

As stated at the WP Pharma on 15/4/25, please find below EL suggestions/proposals for improvement of the following provisions:

Article 6

par. 3a. Where a marketing authorisation is withdrawn for commercial reasons but medicinal product previously placed on the market under that marketing authorisation is allowed **by the Competent Authority of the concerned member state** to remain on the market, all relevant obligations and post-marketing provisions of this Directive and of [revised Regulation 726/2004/EC] shall continue to apply as appropriate until such time as all remaining stock of the medicinal product has expired.

(It is very important that the provision specifies the reason of withdrawal, as well as that the decision to allow these products to remain on the market is within the competences of the member states)

Article 93a Variation based on additional evidence

We are of the opinion that it should be clarified what happens in the case that the MAH does not comply with the obligation to submit a variation application. Is the marketing authorisation suspended/revoked?May the competent authority impose this variation by unilateral act?

ITALY

MAJOR CRITICALITIES

Reading package 1 (General and Authorisations – ST 16051/24)

Proposal for a directive: Articles 5-27 and relevant definitions

- **Article 25 D (*Active substance master file certificate*)**

PROPOSED AMENDMENT:

*1. Marketing authorisation applicants ~~may~~ **should**, 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 Pharmacopeia.*

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

*2. An active substance master file certificate ~~may~~ **should** be granted by the Agency in cases where ~~**the relevant data on**~~ the active substance concerned is not already covered by a monograph of the European Pharmacopeia ~~**or by an active substance master file certificate**~~.*

[…]

COMMENT: We believe that only **two** options should be allowed regarding the ASMF to avoid duplications of work and potentially differing outcomes:

1. Reference to the Active Substance Master File Certificate issued by the EMA in the case of active substances not included in the European Pharmacopoeia
2. Possibility to refer either to the Active Substance Master File Certificate issued by the EMA or to the CEP issued by EDQM in the case of active substances included in the European Pharmacopoeia.

This approach would contribute to remove an extra layer of complexity, optimise the use of already strained Network resources, and ensure harmonisation.

- **Article 4 (Definitions) – Definition no. 20 'kit for radiopharmaceutical preparation'**

PROPOSED AMENDMENT:

*(20) 'kit **for radiopharmaceutical preparation**' means ~~**any preparation**~~ **a medicinal product** to be ~~reconstituted or~~ combined with radionuclides in the final radiopharmaceutical, usually prior to its administration.*

COMMENT: We reiterate this major criticality already raised in various occasions. The definition should be amended as proposed because the kit is one of the four forms of a radiopharmaceutical. Therefore, it can be considered a medicinal product *per se*. It is not correct to refer to a mere reconstitution, since reconstitution is a simple operation that does not change the quality attributes of the medicinal product. Conversely, the marking has such an impact on the medicinal product that it requires the carrying out of a series of regulatory checks that would not be necessary in the case of a mere reconstitution (new specifications, analytical methods, stability data, etc.).

- **Article 16 (Radiopharmaceuticals)**

PROPOSED AMENDMENT:

*1. A marketing authorisation shall be required for radionuclide generators, kits for radiopharmaceutical preparation, and radionuclide precursors, unless they are used as starting material, active substance or intermediate of radiopharmaceuticals covered by a marketing authorisation under Article 5(1). **Member States may, in justified cases, regulate substance-related a temporary exemption from the marketing authorization requirement for radionuclide precursors for diagnostic radiopharmaceuticals, when this***

becomes necessary to ensure an adequate supply of radionuclides throughout the facilities for nuclear medicine provided that the safety and quality profile for the radionuclide precursor is adequately established and assured.
[…]

Proposal for a regulation: Article 177

- **Article 177 amendments to Regulation (EU) No 536/2014**

PROPOSED AMENDMENT: delete the article completely.

COMMENT: This is a red line for us. This article introduces an extra layer of complexity in a procedure that is already structured enough. It also introduces an additional assessment body (the CHMP) other than the Reporting Member State and concerned Member States. However, it should be noted that such body has no mandate either over clinical trials (for which MSs and not EMA are directly responsible) or academic trials. Additionally, if the provision were to be implemented, a new CTIS functionality should be developed. This would further overload a management system, which is already quite burdened.

In particular, we wonder why, despite the overall proposal seems to go in the direction of streamlining the system under the new EMA governance – with the stated aim of optimising the use of resources – it was decided to transfer to the EMA (CHMP) the ERA of investigational medicinal products containing/consisting of GMOs. This choice appears questionable, considering that the CHMP is already heavily overburdened, and will be more so after assuming the competences previously attributed to committees that will be suppressed. Finally, please consider that for the purposes of granting the marketing authorisation, the ERA is currently not decisive. This is even less so in the context of clinical trials: entrusting the ERA to the CHMP would risk having a marginal impact, but would likely result in increasing the length and burden of procedures that - we reiterate it once more - are already complex.

OPTION B: If Article 177 cannot be deleted in its entirety, in the spirit of compromise, we would request the following amendments to paragraphs 4, 5, and 7.

[…]

4. The ~~**Committee for Medicinal Products for Human Use (CHMP) referred to in Article 148 (revised Regulation No (EC) 726/2004]**~~ **Reporting Member State** shall assess the ERA referred to in paragraph 1 in the form of a *scientific opinion. The* ~~***CHMP***~~ ***RMS*** *shall submit its opinion to the competent authority of the Reporting Member State within* ~~*45*~~ *38 days from the validation date referred to in Article 5(3). Where appropriate, the opinion shall include risk mitigation measures. The sponsor shall provide evidence to the Reporting Member State and the Member States Concerned that these measures will be implemented.*

5. *The* ~~***CHMP***~~ ***RMS*** *may request, with justified reasons, via the EU portal (CTIS) additional information from the sponsor regarding the assessment referred to in paragraph 1, which shall be provided only within the period referred to in Article 6, paragraph 5.*

6. *To obtain and review the additional information referred to in paragraph* ~~*6*~~*5, the* ~~***Agency***~~ ***RMS*** *may extend the period referred to in paragraph 5 by a maximum of 31 days. The sponsor shall submit the requested additional information within the period set by the* ~~***Agency***~~ ***RMS****. Where the sponsor does not provide additional information within the period set by the* ~~***Agency***~~ ***RMS****, the application referred to in paragraph 1 shall be deemed to have expired in all Member States concerned. The* ~~***Agency***~~ ***RMS*** *shall inform the* ~~***reporting Member State via the CTIS and the***~~ *Member States concerned* ***via the CTIS*** *about the extension of the period referred to in paragraph 5 in accordance with this paragraph as well as the period set for the sponsor to submit the requested information.*

7. In case of first-in-class products or when a novel question arises during the assessment of the submitted ERA as referred to in paragraph 1, the ~~***Agency***~~ ***RMS*** *shall* ~~*may*~~ *, if* ~~*as*~~ *necessary, consult with bodies that Member States have set up in accordance with Directive 2001/18/EC or Directive 2009/41/EC of the European Parliament and of the Council**. If a consultation is necessary, the technical dossier addressing* in sufficient detail the information specified in Annex III to Directive 2001/18/EC should be included to support the ERA where appropriate.

Please note that Article 138, c.1, point (ca) should be amended accordingly.

Reading package 6 (ST 16051/24)

- Article 36 D (Mutual recognition procedure for national marketing authorisations)

PROPOSED AMENDMENT:

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 concerned Member States and to the applicant ~~***within 90 days after the date of validation of the application***~~.

COMMENT: Read in context, this sentence seems to double the duration of the mutual recognition procedure to 180 days instead of 90 days. Currently, the Applicant requests the Reference Member State (RMS) to update the Assessment Report (AR) 90 days before submitting the dossier to the Concerned Member States (CMS). After these 90 days, at Day -14, the Applicant submits the dossier to the CMSs and the RMS circulates the updated AR and the product information to the CMSs. From that moment the validation phase begins, which lasts 14 days. After these 14 days, at Day 0 the Mutual Recognition procedure begins. It then lasts up to 90 days after this validation phase. If the amendment to this article is maintained, it seems that the Mutual Recognition procedure will take 180 days (90 days to update the AR + 90 days for sending the updated AR and PI for CMS approval).

NETHERLANDS

Regarding the ERA refusal grounds, we have worked on the wording together with the German delegation, as was suggested during the working party. Many thanks to the German colleagues for a fruitful collaboration

Comments of the Netherlands

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Most critical comments

Grounds for refusal regarding ERA

Directive

(70) Marketing authorisation applications for medicinal products in the Union should include an Environmental Risk Assessment (ERA) and **if the ERA identifies a risk to the environment,** risk mitigation measures. If the applicant fails to submit a complete or sufficiently substantiated environmental risk assessment or they do not propose risk mitigation measures to sufficiently address the risks identified in the environmental risk assessment, the marketing authorisation should be refused. **However, in exceptional cases, the applicant can justify that deficiencies can be resolved post authorisation.** ~~**unless the necessary information can be obtained through post-authorisation studies or appropriate risk mitigating measures can be implemented as a condition to marketing authorisation**~~. The ERA should be updated when new data or knowledge about relevant risks become available. **The environmental risk of a medicinal product is not part of the benefit risk balance of a medicinal product.**

Article 44
National marketing authorisation subject to conditions

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

(…)

(ga) in case of Article 47 paragraph 1 point (d) when deficiencies have been declared and adequately justified, ~~the environmental risk assessment suffering from deficiencies at the time of application, or if the risk identified in the environmental risk assessment has not been sufficiently addressed by the applicant,~~ to address the deficiencies within a reasonable time set by the competent authority ~~an agreed timeframe~~ and if required to implement appropriate risk mitigation measures;

Article 47
Refusal of a national marketing authorisation

1. The national marketing authorisation shall be refused if, after verification of the particulars and documentations referred to in Article 6 and subject to the specific requirements laid down in Articles 9 to 14, the view is taken that:

(...)

(d) ~~**the data for**~~ the environmental risk assessment **is incomplete or insufficiently substantiated by the applicant or if the risks identified in the environmental risk assessment have not been sufficiently addressed by the applicant** ~~**submitted by the applicant suffers from major deficiencies, unless post-authorisation environmental risk assessment studies can be requested or the identified risks can be mitigated with appropriate risk mitigation measures. it is considered, taking into account the benefit of the immediate availability of the medicinal product concerned , that those deficiencies shall be addressed with post-authorisation environmental risk assessment studies risks can be mitigated under a post authorisation obligation referred to in Article 44 (1) ga);~~ ~~is incomplete or insufficiently substantiated by the applicant or if the risks identified in the environmental risk assessment have not been sufficiently addressed by the applicant;~~ **unless the applicant has declared and adequately justified that the deficiencies that exist at the time of application can be resolved post-authorisation under an obligation referred to in Article 44 (1)(ga);**

Regulation

Article 12

Committee Opinion

(…)

4. If an opinion is favourable to the granting of the relevant marketing authorisation, the following**s** ~~documents~~ shall be annexed to the opinion:

(…)

(iii)in the case of Article 15 paragraph 1 point (d) when deficiencies have been declared and adequately justified, details on any obligation to address the deficiencies within a reasonable time set by the Agency and if required to implement appropriate risk mitigation measures;

Article 15

Refusal of a centralised marketing authorisation

1. The marketing authorisation shall be refused if, after verification of the particulars and documentation submitted in accordance with Article 6, the view is taken that:

(…)

(d) the environmental risk assessment is incomplete or insufficiently substantiated by the applicant or if the risks identified in the environmental risk assessment have not been sufficiently addressed by the applicant**, unless** ~~**a post-authorisation environmental risk assessment studies can be requested or the identified risks can be mitigated with appropriate risk mitigation measures**~~ **the applicant has declared and adequately justified that the deficiencies that exist at the time of application can be resolved post-authorisation under the obligation referred to in Article 12 (4)(ii)**~~;~~

The default should be that at the time of application the ERA is complete, unless valid reasons exist to obtain missing data post-authorisation. The formulation in the proposal suggests a reversed hierarcy, putting the burden of proof on the competent authorities to justify that ERA data is needed before authorisation because of unacceptable risks.

Our text proposal is aimed at a) preventing the hierarcy is reversed from pre- to post-authorisation and thereby putting the burden of proof on the competent authorities, b) safeguarding that deficiences are resolved post authorisation and c) consistency between Directive and Regulation.

Technical comments

Directive Article 25

Active substance master file ~~certificate~~

(…)

9. The Commission is empowered to adopt delegated acts in accordance with Article 215 to supplement this Directive by specifying, the following:

(aa) the rules for the submission of an application for an active substance master file, outside of the active substance master file certificate route;

We have a proposal to improve the efficiency of the assessment of ASMF submitted outside of the certification route.

Currently, the assessment of ASMFs is insufficient due to decentralised assessment and the voluntary basis for applicants to participate in the worksharing procedure. We therefore very much welcome the concept of ASMF certificates. To further improve the efficiency and futureproof of ASMF assessment, we propose to add to para 9 the possibility to adopt a delegated act specifiying the rules for the submission of an ASMF outside the certification route. This way a legal basis can be created for a coordinated assessment for ASMFs used in multiple application.

Regulation Article 6

Centralised marketing authorisation application

(…)

~~2. For medicinal products that are likely to offer an exceptional therapeutic advancement in the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Union,~~ **~~are intended to be used in relation to potential or declared public health emergency~~** ~~the Agency may, following the advice of the Committee for Medicinal Products for Human Use regarding the maturity of the data related to the development, offer to the applicant a phased review of complete data packages for individual modules of particulars and documentation as referred to in paragraph 1.~~

~~The Agency may at any stage suspend or cancel the phased review, where the Committee for Medicinal Products for Human Use considers that the submitted data are not of sufficient~~

~~maturity or where it is considered that the medicinal product **cannot be used in relation to potential or declared public health emergency**no longer fulfils an exceptional therapeutic advancement. The Agency shall inform the applicant accordingly.~~

Previously the Presidency indicated that the phased review was limited to EU level public health emergencies. However, it seems like the phased review has now been removed entirely.
As stated previously, the Netherlands supports the inclusion of the phased review with the limited scope of potential and declared public health emergencies. We plead to keep the phased review in legislation. This way we can clearly define, allow and restrict the scope of the phased review. Thereby, it will provide a legal basis that will allow EMA to charge a fee. This is important, as phased review is more resource intensive for both EMA and NCAs.
Phased review and TEMA are different instruments. The phased review is used to assess an application for a 'normal' marketing authorisation in modules without granting a preliminary authorisation. In case of a TEMA an authorisation is already granted while the dossier is developed further. We plead to keep both options in the legislation.

Regulation Article 20

Imposed post-authorisation studies

1. After the granting of a marketing authorisation, the Agency may consider that it is necessary that the marketing authorisation holder:

(…)

(d) **conducts a post-authorisation study to improve the safe and effective use of the medicinal product, including treatment optimisation based on clinical experience;.**

Where the Agency considers that any of the post-authorisations studies referred to in points (a) to (**d**~~e~~) is necessary, it shall inform the marketing authorisation holder thereof in writing, stating the grounds for its assessment and shall include the objectives and timeframe for submission and conduct of the study.

(…)

4. Where the opinion of the Agency confirms the need for any of the post-authorisation studies referred to in paragraph 1, points (a) to (**d**~~e~~), to be carried out, the Commission shall vary the marketing authorisation, by means of implementing acts, adopted pursuant to Article 13 to include the obligation as a condition of the marketing authorisation unless the Commission returns the opinion to the Agency for further consideration. For obligations under paragraph 1, points (a) and (b), the marketing authorisation holder shall update the risk management system accordingly.

We have two editorial point for this article:

- Para 1 (d): we propose to add '**including treatment optimisation based on clinical experience'** to align with its mirroring article in the proposed directive art 87 para 1 (ba).
- Para 4: We are of the opinion that point (d) should be added in para 4, in line with para 1.

Directive Article 29

Examination of marketing authorisation application

(…)

3. Where**, in the course of the validation referred to in paragraph 1, point (a),** the competent authority of the Member State considers that the marketing authorisation application is incomplete, or contains ~~critical~~ deficiencies **to the extent** that **this** may prevent the evaluation of the ~~medicinal product~~ **application,** it shall inform the applicant accordingly and shall set a time limit for submitting the missing information and documentation. If the applicant fails to provide the missing information and documentation within the time limit set, the application shall be considered to have been withdrawn **by the applicant**.

(…)

In cases where on examination of an application for a marketing authorisation the competent authority of the Member State considers that the submitted data are not of sufficient quality or maturity for the completion of the examination of the application, the examination can be terminated within 90 days of the **date of** validation of the application.

Prior to the termination, t~~T~~he 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 applicant accordingly and set a time limit to address the deficiencies. The application shall be suspended until the applicant addresses the deficiencies. If the 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** application shall be considered as withdrawn **by the applicant**.

In line with Article 34 para 4 of the proposed Directive, we propose to include 'withdrawn by the applicant' in para 3 and 4. This would prevent the administrative burden for competent authorities of drawing up withdrawal reports.

Directive Article 34

Decentralised procedure for national marketing authorisations

(…)

4. In cases where on examination of an application for a marketing authorisation the competent authority of the reference Member State for the decentralised procedure considers that the submitted data are not of sufficient quality or maturity for the completion of the examination of the application, the examination can be terminated within ~~90~~ 70 days of ~~the completion~~ **the date of** the validation of the application.

(…)

Paragraph 4 addresses the total total time period (for both applicant and NCA) to resolve an immature dossier. This article describes 90 days but Directive article 29 para 5 mentions 90 days, raising confusion on the applicable timelines for DCPs. It is therefore important that articles 29(4) and art 34(4) are aligned and follow the same timelines. We prefer the 90 days of the initial proposal.

Directive Article 36

Mutual recognition procedure for national marketing authorisations

(…)

5. ~~If **any of** the competent authorities of the Member States concerned so require, the marketing authorisation holder shall request the competent authority of the reference Member State for the mutual recognition procedure to update the assessment report drawn on the medicinal concerned by the application. In that case, the reference Member State shall update the assessment report within 90 days after **the completion date of the** validation of the application. If **none of** the competent authorities of the Member States concerned do not require the update of the assessment report, the reference Member State shall provide the assessment report within 30 days **after the completion date of the validation of the application** .~~ **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 concerned Member States and to the applicant within 90 days after the date of validation of the application.**

(…)

We propose a different wording for paragraph 5, to further clarify the timing of preparing or updating the assessment report by the RMS. This step takes place before submission of the dossier

to the CMS and thus before validation of the mutual recognition application. Otherwise, the timelines for the overall procedure will double to 180 days: 90 days for the RMS to send the assessment report and 90 days for the CMS to approve the assessment report (see paragraph 6).

Currently, the Mutual Recognition Procedure is as follows:

- If any of the competent authorities of the Member States concerned so require**,** an applicant requests the Reference Member State (RMS) to update the Assessment Report (AR) **90 days before submission** to the Concerned Member State (CMS).

- **14 days before the validation of the application**, the applicant submits the dossier to the Concerned Member State. The RMS circulates the assessment report together with the approved summary of product characteristics, labelling and package leaflet, to the CMS and the CMS can validate the application.

- After this, the Mutual Recognition Procedure starts. The time line for the procedure is (at maximum) 90 days.

Directive Article 37

Coordination group for decentralised and mutual recognition procedures

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

(…)

(e) to reach agreement on the harmonisation of summary of product characteristics, in accordance with Article 40.

(…)

From the agreed change to Directive article 40 paragrpah 3, we conclude that the coordination group is allowed to take decisions on the harmonisation of SmPCs itself and not only on the list. Therefore, we propose to add this compentence in para 1 of article 37.

ROMANIA

We are sending you one short proposal with regards the *pharmacovigilance cluster*, for your attention.

In ”Article **106** - *Recording and reporting of suspected adverse reactions by Member States*”, paragraph **5**, **RO** would like to reiterate the suggestion to replace ”*error associated with the use of a medicinal product*” with ”use of the product outside the terms of the marketing authorization (such as off-label use, overdose, misuse, abuse, medication errors)” in order to capture all the situations of use outside the MA and not only from medication errors as currently stated.
This proposal is in line with the amendment proposed by the PRES at art 105, paragraph 1, replacing the term "off-label use" with "use outside the terms of marketing authorization".

SPAIN

Please, find below our red line on ***Authorisation cluster***:

Article 177 OMG proposed Regulation:

ES cannot support the centralisation of clinical trials for GMOs and considers that clinical trials information system (CTIS) with GMOs should be a left to Member states. Furthermore, we think that including the opinion of the CHMP for each GMO to assess the ERA is excessive and will be a heavy burden for the CHMP.

SWEDEN

AUTHORISATIONS

Art. 9 D

SE propose two additions in paragraph 2

Proposal

For the purpose of demonstrating the equivalence as referred to in paragraph 1, the applicant shall **for systemically acting products** submit to the competent authorities **bio**equivalence studies, or a justification as to why such studies were not performed and demonstrate that the generic medicinal product meets the relevant criteria set out in the appropriate detailed guidelines. **For locally applied and locally acting products, the applicant shall submit to the competent authorities studies demonstrating therapeutic equivalence as set out in the appropriate detailed guidelines.**

Justification

SE share the concerns of DE that we should not weaken the criteria for generic authorisations. Locally acting/locally applied (LALA) products are today considered under Article 10(3) hybrid application as bioequivalence studies are not applicable. However, we find it logical to include all generic applications for the same active substance, strength and form under Article 9, regardless of the nature of the underlying data for showing equivalence, so we do not agree to mention "bioequivalence" in Article 9(1). To avoid different national interpretations or discussions with applicants, we find it important that the legislation is very clear on this subject. We therefore propose some additional wording to Article 9(2) above.

Art. 19 D

In-vitro diagnostic medical devices need to be included in paragraphs 1, 2, 3 and 4 to correspond to the heading of the article (*Medicinal products in exclusive use with medical devices* ***or in-vitro diagnostic medical devices).***

The second 'medical' before device in para 2 should be deleted.

We propose that the wording 'the results of the conformity assessment or the conformity assessment' is changed to 'an EU declaration of conformity and an EU certificate issued'. The proposed changes is an effort to harmonise the wordings with the MDR and IWDR.

Para 6: the reference to the regulation 2017/746 should be deducted since the paragraph not applicable to the products regulated in that regulation (which is in-vitro diagnostic medical devices).

Art. 22 D

SE proposes that the first part of the first sentence in paragraph 3 should be deducted ('Where the ERA identifies a risk to the environment).

With the added phrasing in the first sentence, the article loses its original intent. The intent is to harmonise with other legislative frameworks and have a *one substance one assessment* approach. The substances in the directives mentioned in the article, constitutes a problem in the environment. It is therefore reasonable to demand risk mitigation measures from the pharmaceutical industry. When identifying risk in the environmental risk assessment one major component is the amount of use of the pharmaceutical. This may mean that many of the substances listed in the directives mentioned may not constitute a risk in the ERA-assessment. Nonetheless, mitigation measures are justified and needed in all industries including the pharmaceutical industry.

Art. 40

Regarding paragraph 3: SE have no objections to the compromise proposal to let the coordination group deal with harmonisation of SmPCs but the **article needs reformulation to describe the procedure and get a legally binding decision**. Without a legally binding decision, as we have today with a commission decision issued after an article 30 referral to CHMP, we lack a tool to enforce implementation. This is necessary, as originator companies won't profit from making it easier to approve generics when their SmPC is harmonized.

FR also brought this up at the Council working party meeting on 15 April and SE supports the intervention made by FR.

Art. 44 D

SE propose that paragraph (ga) should be deleted.

This addition makes it possible for the marketing authorisation holder to not enclose complete environmental risk assessments at the time of application for a centralised marketing authorisation. This is the situation today. Only a few marketing authorisation applications contain a complete environmental risk assessment and when they are incomplete, the national competent authorities cannot do anything about it.

Art. 47 D

SE propose that all additions in the latest compromised text should be deleted.

The additions make it possible for the marketing authorisation holder to not enclose complete environmental risk assessments at the time of application for a centralised marketing authorisation. This is the situation today. Only a few marketing authorisation applications contain a complete environmental risk assessment and when they are incomplete, the national competent authorities cannot do anything about it.

Art. 15 Reg.

SE propose that the added text in paragraph 1 d is deleted. This addition makes it possible for the marketing authorisation holder to not enclose complete environmental risk assessments at the time of application for a centralised marketing authorisation. This is the situation today. Only a few marketing authorisation applications contain a complete environmental risk assessment and when they are incomplete, the national competent authorities cannot do anything about it.

COMMENTS FROM
SLOVENIA

ANNEX

1st READING PACKAGE:
GENERAL AND AUTHORISATIONS
SUBJECT MATTER AND SCOPE

RECITALS

REVISED DIRECTIVE

(1) The Union general pharmaceutical legislation was established in 1965 with the dual objective of safeguarding public health and harmonising the internal market for medicines. It has developed considerably since then, but these overarching objectives have guided all revisions. The legislation governs the granting of marketing authorisations for all medicines 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 medicines with a positive benefit-risk balance after assessment of their quality, safety and efficacy.

(5) The essential aim of any rules governing the authorisation, manufacturing, supervision, distribution and use of medicinal products must be 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.

(6) The regulatory framework for medicinal products 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.

(12) The definitions and scope of Directive 2001/83/EC 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.

(14) The determination of whether a product falls within the definition of a medicinal product must 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.

(15) In order to take account both of the emergence of new therapies and of 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. With the same objective of clarifying situations when a product fully falls within the definition of a medicinal product and also meet the definition of other regulated products, the rules for medicinal products under this Directive apply. Furthermore, to ensure the clarity of applicable rules, it is also appropriate to improve the consistency of the terminology of the pharmaceutical legislation and clearly indicate the products excluded from the scope of this Directive.

(16) The new definition for a substance of human origin (SOHO) by the [SoHO Regulation] 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, may become SoHO derived medicinal products, other than ATMPs, when the SoHO is subject to an industrial process involving systematisation, reproducibility and operations performed on a routine basis or batch-wise resulting in a product of standardised consistency. When a process concerns extraction of an active ingredient from the SoHO, other than tissues and cells, or a transformation of a SoHO, other than tissues and cells, by changing its inherent properties, this should also be considered a SoHO derived medicinal product. When a process concerns concentrating, separating or isolating elements in the preparation of blood components, this should not be considered as changing their inherent properties.

(17) For avoidance of doubt, the safety and quality of human organs intended for transplantation are regulated only by Directive 2010/53/EU of the European Parliament and of the Council3, and the safety and quality of substances of human origin intended for medically assisted reproduction are regulated only by [SoHO Regulation or if not in force, Directive 2004/23/EC].

(18) Advanced therapy medicinal products that are prepared on a non-routine basis according to specific quality standards, and **then** 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 for an individual patient, should be excluded from the scope of this Directive whilst at the same time ensuring that relevant Union rules related to quality and safety are not undermined ('hospital exemption'). Experience has shown that there are great differences in the application of hospital exemption among Member States. To improve the application of hospital exemption this Directive introduces measures for collection, reporting of data as well as review of these data yearly by the competent authorities and their publication by the Agency in a repository. Furthermore, the Agency should provide a report on the implementation of hospital exemption on the basis of contributions from Member States in order to examine whether an adapted framework should be established for certain less complex ATMPs that have been developed and used under the hospital exemption. When an authorisation for the manufacturing and use of an ATMP under hospital exemption is revoked because of safety concerns, the relevant competent authorities shall inform the competent authorities of other Member States.

REVISED REGULATION

(6) For the sake of clarity, it is necessary to replace Regulation (EC) No 726/2004 of the European Parliament and of the Council3 with a new Regulation.

(7) Veterinary medicinal products are governed by Regulation (EU) No 2019/6 of the European Parliament and of the Council4. These medicinal products are outside the scope of this Regulation, even if certain provisions regarding the governance and general tasks of the Agency set out in this Regulation apply to these medicinal products. The specific tasks of the Agency in respect to veterinary medicinal products are laid down in Regulation 2019/6 and Regulation 470/2009 of the European Parliament and of the Council.

(8) The scope of centrally authorised medicinal products has been adapted to the realities of the market and technological development as well as the need to ensure a centralised assessment for certain categories of medicinal products. In the light of the Commission's report6 on the experience gained, it has proved necessary to improve the operation of the marketing authorisation procedures for the placing of medicinal products on the Union market and to amend certain administrative aspects of the European Medicines Agency. In addition, the regulatory framework should be adapted to the current market conditions and economic reality, while continuing to safeguard a high level of protection of public health and the environment. The conclusions of that report call for corrections to some of the operating procedures and require adaptations to take account of scientific and technological development. It also emerges from the report that the general principles previously established which govern the centralised marketing authorisation procedure ('centralised procedure') should be maintained.

(9) As to the scope of this Regulation, the authorisation of antimicrobials is, in principle, in the interest of patients' health at Union level and therefore it should be made possible to authorise them at Union level.

(10) With a view to maintain a high-level of scientific evaluation for new medicinal products and medicinal products that will serve the entire Union population, the centralised procedure should be mandatory for high-technological medicinal products, particularly those resulting from biotechnological processes, priority antimicrobials, orphan medicinal products, paediatric use medicinal products and any medicinal product that includes an active substances not authorised before the last important change to the scope of the centralised procedure in 2004.

(11) As regards medicinal products for human use, optional access to the centralised procedure should also be foreseen in cases where use of a single procedure produces added value for the patient. The centralised procedure should remain optional for medicinal products which, although not belonging to the categories of products to be authorised by the Union, are nevertheless therapeutically innovative. It is also appropriate to allow access to this procedure for medicinal products which, although not innovative, may be of benefit to society or to patients, including paediatric patients, if they are authorised from the outset at Union level, such as certain medicinal products which can be supplied without a medical prescription. This option may be extended to generic and biosimilar medicinal products authorised by the Union, provided that this in no way undermines either the harmonisation achieved when the reference medicinal product was evaluated or the results of that evaluation. At the same time, to ensure wide availability of generic medicinal products, those medicinal products may be authorised in any case by the competent authorities of the Member States, even if they are based on a centrally authorised reference medicinal product.

(154) This Regulation is based on the double legal basis of Article 114 and Article 168(4), point (c), TFEU. It aims at achieving an internal market as regards medicinal products for human use, taking as a base a high level of protection of health. At the same time, this Regulation sets high standards of quality and safety for medicinal products in order to meet common safety concerns as regards these products. Both objectives are being pursued simultaneously. These two objectives are inseparably linked and one is not secondary to another. Regarding Article 114 TFEU, this Regulation establishes a European Medicines Agency and provides specific provision with regard to the central authorisation of medicinal products, therefore ensuring the functioning of the internal market and the free movement of medicinal products. Regarding Article 168(4), point (c), TFEU, this Regulation sets high standards of quality and safety for medicinal products.

(155) This Regulation respects the fundamental rights and observes the principles recognised in particular by the Charter of Fundamental Rights of the European Union and notably human dignity, the integrity of the person, the rights of the child, respect for private and family life, the protection of personal data and the freedom of art and science.

(156) The objective of this Regulation is to ensure the authorisation of high quality medicinal products, including for paediatric patients and patients suffering from rare diseases throughout the Union. Where this objective cannot be sufficiently achieved by the Member States but can rather, by reason of its scale, 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 Regulation does not go beyond what is necessary in order to achieve that objective.

REVISED DIRECTIVE

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, control and use of medicinal products for human use.

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

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

4. In cases where~~, taking into account all its characteristics,~~ a product falls within the definition of a 'medicinal product' and within the definition of a product covered by other Union law and there is a conflict between this Directive and other Union law, the provisions of this Directive shall prevail.

5. The Directive shall not apply to:

(a) medicinal products prepared in a pharmacy in accordance with a medical prescription for an individual patient ('magistral formula');

(b) medicinal product prepared in a pharmacy in accordance with a **European** pharmacopoeia **or with the pharmacopoeia of a Member State** and intended to be supplied directly to the patients served by the pharmacy in question **or to the hospitalserved by the pharmacy or another pharmacy which intends to supply the medicinal prodeucts directly to the patients** ('officinal formula');

(c) investigational medicinal product as defined in Article 2, paragraph 5, of Regulation (EU) No 536/2014

~~**(d) SoHO preparations as defined in Article 3 (37) of Regulation (EU) No 2024/1938, unless the requirements of a SoHO derived medicinal product are met**~~. **substances of human origin, unless they fall within the definition of an advanced therapy medicinal product or a SoHO-derived medicinal product other than ATMPs.**

6. Medicinal products referred to in paragraph 5, point (a), may be prepared ~~in duly justified cases~~ in advance by a pharmacy ~~serving a hospital~~, on the basis of the estimated medical prescriptions ~~within that hospital~~ for the following ~~seven days~~ **four weeks**.

7. Member States shall take the necessary measures to develop the production and use of medicinal products derived from substances of human origin coming from voluntary unpaid donations **in accordance with Article 54 of Regulation (EU) No 2024/1938**.

8. ~~This Directive and all Regulations referred to therein shall be without prejudice to the application of national legislation prohibiting or restricting the use of any specific type of substance of human origin or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from these animal cells or substances of human origin, on grounds not dealt with in the aforementioned Union law. The Member States shall communicate the national legislation concerned to the Commission.~~

9. The provisions of 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 and social conditions.

10. This Directive shall not affect the application of national legislation prohibiting or restricting the following:
    (a) the sale, supply or use of medicinal products as contraceptives or abortifacients;
    (b) the use of any specific type of substance of human origin or animal cells, on grounds not dealt with in the aforementioned Union law;
    (c) the sale, supply or use of medicinal products containing, consisting of or derived from these animal cells or substances of human origin, on grounds not dealt with in Union law.

The Member States shall communicate the national legislation concerned to the Commission.

Article 2

Advanced therapy medicinal products prepared under hospital exemption

1. By way of derogation from Article 1(1), only this Article shall apply to advanced therapy medicinal products prepared on a non-routine basis in accordance with the requirements set in paragraph 3 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 for an individual patient ('advanced therapy medicinal products prepared under hospital exemption').

2. The manufacturing of an advanced therapy medicinal product prepared under hospital exemption shall require an approval by the competent authority of the Member State ('hospital exemption approval'). Member States shall notify any such approval, as well as subsequent changes, 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 advanced therapy medicinal products prepared under hospital exemption comply with the requirements equivalent to the good manufacturing practices and traceability for advanced therapy medicinal products referred to in Articles 5 and 15 of Regulation (EC) No 1394/2007[1] respectively, and with pharmacovigilance requirements equivalent to those provided for at Union level pursuant to [revised Regulation (EC) No 726/2004].

4. Member States shall ensure that data on the use, safety and the efficacy of advanced therapy medicinal products prepared under hospital exemption is collected and reported **in an aggregated manner** by the hospital exemption approval holder to the competent authority of the Member State at least annually. The competent authority of the Member State shall review such data and shall verify the compliance of advanced therapy medicinal products prepared under hospital exemption with the requirements referred to in paragraph 3.

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

6. The competent authority of the Member State shall transmit the **available** data related to the use, **incuding the indication and the location of the use, as well as** ~~,~~ safety and efficacy of an advanced therapy medicinal product prepared under the hospital exemption approval 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 that data**, including the mechanism for electronic submission**.

7. The Commission shall adopt implementing acts to specify the following:
   (a) details of the application for the approval of hospital exemption referred to in paragraph 1, second subparagraph, including the evidence on quality, safety and efficacy of the advance therapy medicinal products prepared under hospital exemption for the approval and the subsequent changes;

[1] 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. 1).

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

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

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

Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 214(2).

8. The Agency shall provide to the Commission a report on the experience acquired with the hospital exemption approvals on the basis of contributions from Member States and the data referred to in paragraph 4. The first report shall be provided three years after [OP please insert the date =18 months after the date of entering into force of this Directive] and then every five years thereafter.

Article 3

Exceptions under certain circumstances

1. A Member State may, in order to fulfil special needs, exclude from the scope of this Directive

(a) medicinal products supplied in response to a bona fide unsolicited order, prepared in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under their direct personal responsibility

(b) **medicinal products supplied in response to unavailability of the medicinal product due withdrawal, suspension, cessation of marketing or shortages, if the unavailability or the shortage cannot be prevented or resolved through Union coordination in accordance with chapter X of [revices directive 2001/83] ~~of authorised medicinal products~~**.

However, in such case Member States shall encourage healthcare professionals and patients to report data on the safety of the use of such products to the competent authority of the Member State in accordance with Article 97.

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

2. Without prejudice to Article 30 of [revised Regulation (EC) No 726/2004], 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.

3. Member States shall ensure that 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 in response to the suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm. Such provisions shall apply whether or not a national or a centralised marketing authorisation has been granted.

4. Liability for defective products, as provided for by [Council Directive 85/374/EEC[2] – OP please replace reference by new instrument COM(2022) 495 when adopted], shall not be affected by paragraph 3.

[2] Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States, concerning liability for defective products (OJ L 210, 7.8.1985, p. 29).

REVISED REGULATION

CHAPTER I
SUBJECT MATTER, SCOPE AND DEFINITIONS

Article 1
Subject matter and scope

This Regulation lays down Union procedures for the authorisation, supervision and pharmacovigilance of medicinal products for human use at Union level, establishes rules and procedures at Union and at Member State level relating to the security of supply of medicinal products and lays down the governance provisions of the European Medicines Agency ('the Agency') established by Regulation (EC) No 726/2004 which shall carry out the tasks relating to medicinal products for human use that are laid down in this Regulation, Regulation (EU) No 2019/6 and other relevant Union legal acts.

This Regulation shall not affect the powers of Member States' authorities as regards setting the prices of medicinal products or their inclusion in the scope of the national health system or social security schemes on the basis of health, economic and social conditions. Member States may choose from the particulars shown in the marketing authorisation those therapeutic indications and pack sizes which will be covered by their social security bodies.

Article 3
Centrally authorised medicinal products

1. A medicinal product listed in Annex I shall only be placed on the Union market if a marketing authorisation for that medicinal product has been granted by the Union in accordance with this Regulation ('centralised marketing authorisation').

2. Any medicinal product not listed in Annex I, may be granted a centralised marketing authorisation in accordance with this Regulation, if the product meets at least one of the following requirements:

(a) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of marketing authorisation in accordance with this Regulation is in the interest of patients' health at Union level, including as regards antimicrobial resistance and medicinal products for public health emergencies;

(b) it is a medicinal product intended solely for paediatric use.

3. Homeopathic medicinal products shall not be granted a marketing authorisation in accordance with this Regulation.

4. The Commission shall grant and supervise centralised marketing authorisations for medicinal products for human use in accordance with Chapter II.

~~5. The Commission is empowered to adopt delegated acts in accordance with Article 175 to amend Annex I to adapt it to technical and scientific progress.~~

Article 180

Transitional provisions

(X) Marketing authorisations of human medicinal products authorised in accordance with Directive 2001/83/EC shall be deemed to have been issued in accordance with this [revised] Directive, irrespective of whether those products are covered by Annex I to [Revised Regulation (EC) No 726/2004.

Article 4

*Member State authorisation of generics**, ~~and~~ biosimilars,** *of centrally authorised medicinal products*

A generic **and a biosmilar** medicinal product of a reference medicinal product authorised by the Union may be authorised by the competent authorities of the Member States in accordance with [revised Directive 2001/83/EC] under the following conditions:

(a) the application for marketing authorisation is submitted in accordance with Article 9 **or 11** of [revised Directive 2001/83/EC];

(b) the summary of product characteristics and the package leaflet are in all relevant respects consistent with that of the medicinal product authorised by the Union**:**

(c) the reference medicinal product is not an advancded therapy medicinal product

Point (b), first subparagraph, shall not apply to those parts of summary of product characteristics and package leaflet referring to indications, posologies, pharmaceutical forms, methods or routes of administration or any other way in which the medicinal product may be used which were still covered by a patent or a supplementary protection certificate for medicinal products at the time when the generic medicinal product was marketed and where the applicant for the generic **or biosimilar** medicinal product has requested not to include this information in their marketing authorisation.

CHAPTER V
PRE-AUTORISATION REGULATORY SUPPORT

Article 61

Scientific recommendation on regulatory status

1. For products under development which may fall within the categories of medicinal products to be authorised by the Union listed in Annex I, a developer or a competent authority of the Member States may submit a duly substantiated request to the Agency for a scientific recommendation with a view to determining on scientific grounds whether the concerned product is potentially a 'medicinal product', including an 'advanced therapy medicinal product' as defined in Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council[3].

[3] 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).

The Agency shall deliver its recommendation within 60 days of receiving such a request, which shall be extended by an additional 30 days where a consultation in accordance with paragraph 2 is required.

2. When forming the recommendation referred to in paragraph 1, the Agency shall consult, where appropriate, relevant advisory or regulatory bodies established in other Union legal acts in related fields. In the case of products which are based on substances of human origin, the Agency shall consult the Substances of Human Origin (SoHO) Coordination Board as established in Regulation (EU) No [*reference to be added after adoption cf. COM(2022)338 final*].

The advisory or regulatory bodies consulted shall reply to the consultation within 30 days of receipt of the request.

Where as a result of such consultation it is identified that the product is not considered to be a medicinal product but may fall within the scope of another Union legislation, the Agency recommendation may advise the developer or the competent authority to engage with the relevant advisory or regulatory bodies.

The Agency shall publish summaries of the recommendations delivered in accordance with paragraph 1, after deletion of all information of a commercially confidential nature.

Article 62

Decision on regulatory status

1. In the case of duly substantiated disagreement with the Agency's recommendation, in accordance with Article 61(2), a Member State may request the Commission to decide whether the product is a product referred to in Article 61(1).

The Commission may initiate the procedure referred to in the first subparagraph on its own initiative.

2. The Commission may ask the Agency for clarifications or refer the recommendation back to the Agency for further consideration where a Member State's substantiated request raises new questions of a scientific or technical nature or on its own initiative.

3. The decision of the Commission referred to in paragraph 1 shall be adopted by means of implementing acts, in accordance with the examination procedure referred to in Article 173(2), taking into account the scientific recommendation of the Agency.

ANNEX I
MEDICINAL PRODUCTS TO BE AUTHORISED BY THE UNION

1. Medicinal products developed by means of one of the following biotechnological processes:
   – recombinant nucleic acid technology;
   – controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells.

2. Advanced therapy medicinal products as defined in Article 2 of Regulation (EC) No 1394/2007.

3. Medicinal products for human use containing a~~n~~ **new** active substance which on 20 May 2004 was not authorised in the Union, excluding allergen products or herbal medicinal products, which shall in any case not be authorised by the Union.

4. Medicinal products that are designated as orphan medicinal products pursuant to this Regulation.

5. Medicinal products authorised in accordance with a paediatric use marketing authorisation.

6. Priority antimicrobials as referred to in Article 40.

REVISED DIRECTIVE

Article 4
Definitions

(1) 'medicinal product' means ~~any substance or combination of substances that fulfils at least one of the following conditions~~:

(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, e.g. tissues and cells, human blood, human secretions and human blood products;

(b) animal, e.g. whole animals, animal organs and parts thereof, animal tissues and cells, animal secretions, toxins, extracts, animal blood and animal blood products;

(c) vegetal, e.g. plants, including algae, parts of plants, plant secretions and exudates, extracts;

(d) chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis;

(e) micro-organisms, e.g. bacteria, viruses and protozoa;

(f) fungi, including 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 make a medical diagnosis;

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

(4a) ‘intermediate product’: means any product that has been prepared by the manufacturer with the intention of further processing to obtain the active substance and/or finished product.

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

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

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

(8) ‘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;

(27) ‘immunological medicinal product’ means:

(a) any vaccine**, toxin,** ~~or~~ allergen **medicinal** product, or **any other medicinal product eliciting an active and specific immune response**

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

(28) 'vaccine’ means any medicinal product that is intended to elicit an **active and specific** immune response for prevention, including post exposure prophylaxis, and for treatment of diseases caused by an infectious agent;

(29) 'gene therapy medicinal product' means a medicinal product, except vaccines against infectious diseases, that contains or consists of:

(a) a substance or a combination of substances intended to edit the host genome in a sequence-specific manner or that contain or consists of cells **or tissues** 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 transcription or translation of the transferred genetic materials or that contain or consists of cells subjected to these modifications;

(30) '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 subject 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.

(31) 'SoHO-derived medicinal product other than ATMPs' means any medicinal product containing, consisting of or deriving from a substance of human origin (SoHO), as defined in Regulation [SoHO Regulation], 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;

Authorisations

RECITALS

REVISED DIRECTIVE

(1) The Union general pharmaceutical legislation was established in 1965 with the dual objective of safeguarding public health and harmonising the internal market for medicines. It has developed considerably since then, but these overarching objectives have guided all revisions. The legislation governs the granting of marketing authorisations for all medicines 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 medicines with a positive benefit-risk balance after assessment of their quality, safety and efficacy.

(2) The most recent comprehensive revision took place between 2001 and 2004 while targeted revisions on post-authorisation monitoring (pharmacovigilance) and on falsified medicines 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. Moreover, some patients may not benefit from innovation because medicines may be unaffordable or not placed on the market in the Member State concerned. There is also a greater awareness of the environmental impact of medicines. More recently, the COVID-19 pandemic has stress tested the framework.

(3) This revision is part of the implementation of the Pharmaceutical strategy for Europe and aims to promote innovation, in particular for unmet medical needs, while reducing regulatory burden and the environmental impact of medicines; ensure access to innovative and established medicines 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 keeps medicines affordable for health systems while rewarding innovation.

(19) This Directive should be without prejudice to the provisions of Council Directive 2013/59/Euratom[4], including with respect to justification and optimisation of 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 have to notably respect that Directive's requirements that exposures of target volumes are to be individually planned, and their delivery appropriately verified taking into account that doses to non-target volumes and tissues are to be as low as reasonably achievable and consistent with the intended therapeutic purpose of the exposure.

(21) Marketing authorisation decisions should be taken on the basis of the objective scientific criteria of 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 medicinal products.

(22) The particulars and documentations that are to accompany an application for marketing authorisation for a medicinal product demonstrate that the therapeutic efficacy of the product overweight potential risks. The benefit-risk balance of all medicinal products will be assessed when they are placed on the market, and at any other time the competent authority deems appropriate.

(23) As market forces alone have proven insufficient to stimulate adequate research into, and the development and authorisation of, medicinal products for the paediatric population, a system of both obligations and rewards and incentives has been put in place.

[4] 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).

(24) 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.

(27) Certain particulars and documentation that are normally to be submitted with an application for a marketing authorisation should not be required if a medicinal product is a generic medicinal product or a similar biological medicinal product (biosimilar) that is authorised or has been authorised in the Union. Both generic and biosimilar medicinal products are important to ensure access of medicinal products to a wider patient population and create a competitive internal market. In a joint statement 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 its reference product (or vice versa) or replaced by another biosimilar of the same reference product.

(29) For generic medicinal products only the equivalence of the generic medicinal product with the reference medicinal product has to be demonstrated. For biological medicinal products, only the results of comparability tests and studies are provided to the competent authorities. For hybrid **and bio-hybrid** medicinal products i.e. in cases where the medicinal product does not fall within the definition of a generic **or biosimilar** medicinal product or has changes in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference medicinal product, the results of the appropriate non-clinical tests or clinical studies shall 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.

(30) Regulatory decision-making on the development, authorisation and supervision of medicines may be supported by access and analysis of health data, including real world data i.e. health data generated outside of clinical studies, where appropriate. The competent authorities should be able to use such data, including via the European Health Data Space interoperable infrastructure.

(31) Directive 2010/63/EU of the European Parliament and of the Council[5] lays down provisions on the protection of animals used for scientific purposes based on the principles of replacement, reduction and refinement. 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 those principles of replacement, reduction and refinement, where they concern the care and use of live animals for scientific purposes, and should 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 EMA and ICH guidelines. In particular, the marketing authorisation applicant and the marketing authorisation holder should take into account the principles laid down in Directive 2010/63/EU, including, where possible, use new approach methodologies in place of animal testing. These can include but are not limited to: in vitro models, such as microphysiological systems including organ-on-chips, (2D and 3D-) cell culture models, organoids and human stem cells-based models; in silico tools or read-across models.

(32) Procedures should be in place to facilitate joint animal testing, wherever possible, in order to avoid unnecessary duplication of testing using live animals covered by 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.

[5] 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).

(33) 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 these trials were conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to the provisions of Regulation (EU) 536/2014 of the European Parliament and of the Council[6].

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

(67) The provision of information to healthcare professionals and to patients on the appropriate use, storage and disposal of antimicrobials is a joint responsibility of marketing authorisation holders and of Member States who should ensure appropriate collection system for all medicinal products.

(68) While this Directive restricts the use of antimicrobials by setting certain categories of antimicrobials under prescription status, due to the growing antimicrobial resistance in the Union, competent authorities of the Member States should consider further measures for example expanding the prescription status of antimicrobials or the mandatory use of diagnostic tests before prescription. 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.

[6] 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).

(69) 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 from their manufacturing, 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 Regulation complement the main environmental legislation, in particular the Water Framework Directive (2000/60/EC[7]), the Environmental Quality Standard Directive (2008/105/EC[8]) the Groundwater Directive (2006/118/EC[9]), the Urban Wastewater Treatment Directive (91/271/EEC[10]), the Drinking Water Directive (2020/2184[11]) and the Industrial Emissions Directive (2010/75/EU[12]).

(70) Marketing authorisation applications for medicinal products in the Union should include an Environmental Risk Assessment (ERA) and risk mitigation measures. If the applicant fails to submit a complete or sufficiently substantiated environmental risk assessment or they do not propose risk mitigation measures to sufficiently address the risks identified in the environmental risk assessment, the marketing authorisation should be refused **unless the necessary information can be obtained through post-authorisation studies or appropriate risk mitigating measures can be implemented as a condition to marketing authorisation**. The ERA should be updated when new data or knowledge about relevant risks become available.

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7 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).

8 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).

9 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).

10 Council Directive 91/271/EEC of 21 May 1991 concerning urban waste-water treatment (OJ L 135, 30.5.1991, p. 40).

11 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 (recast) (OJ L 435, 23.12.2020, p. 1).

12 Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control) (recast) (OJ L 334, 17.12.2010, p. 17).

(71) Marketing authorisation applicants should take into account environmental risk assessment procedures of other EU legal frameworks that may apply to chemicals dependent on their use. Further to this Regulation, there are four main other frameworks: (i) Industrial chemicals (REACH, (Regulation (EC) No 1907/2006); (ii) Biocides (Regulation (EC) No 528/2012); (iii) Pesticides (Regulation (EC) No 1107/2009); and (iv) Veterinary medicines (Regulation (EU) 2019/6)). As a part of the Green Deal, the Commission has proposed a 'one-substance one-assessment' (OS-OA) approach for chemicals[13], in order to increase the efficiency of the registration system, reduce costs and unnecessary animal testing.

(72) The emissions and discharges of antimicrobials to the environment from manufacturing sites may lead to antimicrobial resistance ("AMR"), which is a global concern regardless where the emissions and discharges take place. Therefore, the ERA scope should be extended to cover the risk of AMR selection during the entire life cycle of antimicrobials, including manufacturing.

(73) The proposal also includes 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 application.

(74) For medicinal products authorised prior to October 2005, without any ERA, specific provisions should be introduced to set up a risk based prioritisation programme for the ERA submission or update by the market authorisation holders. **For ~~medicinal~~ generic, biosimilar, hybrid and bio-hybrid medicinal products and fixed-dose combinations of active substances, for which the reference medicinal product has been authorised before 30 October 2005, and which are included in this programme, the ERA should be submitted after the outcome of the ERA of such reference medicinal product is made publicly available by the Agency.**

[13] Communication from the Commission to the European Parliament, the European Council, the Council, the European Economic and Social Committee and the Committee of the Regions, The European Green Deal, Brussels (2019), COM(2019) 640 final.

(79) As a general rule, risk management plans for generic and biosimilar medicinal products should not be developed and submitted, considering that the reference medicinal product has such a plan, except in specific cases, where a risk management plan should be provided. Furthermore, as a general rule a marketing authorisation should be granted for an unlimited period; exceptionally, one renewal may be decided only on justified grounds related to the safety of the medicinal product. **In addition the risk management plan for hybrid and bio-hybrid medicinal products should be limited to the differences between this medicinal product and the reference medicinal product, as indicated in the application for the marketing authorisation, 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 application.**

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

(82) For products that combine a medicinal product and a medical device**, including in vitro diagnostics,** the applicability of the two respective regulatory frameworks should be specified and the appropriate interaction between the **three** ~~two~~ applicable regulatory frameworks should be ensured. The same should apply to combinations of medical products and products other than medical devices.

(83) 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**, including in vitro diagnostics,** or of combinations of a medicinal product with a product other than a medical device, the marketing authorisation applicant shall submit data establishing the safe and effective use of the integral combination of the medicinal product with the medical device**, including in vitro diagnostics,** 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 taking into account the suitability of the use of the medicinal product together with the medical device**, in vitro diagnostics** or the other product.

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

(85) The Directive also clarifies that a medical device that is part of an integral combination has to comply with the general safety and performance requirements set out in Annex I of Regulation (EU) 2017/745 of the European Parliament and of the Council[14]. A medical device in exclusive use with a medical device needs to meet all of the requirements of Regulation (EU) 2017/745. A medicinal product in exclusive use with a medical device that is not ancillary to that of the medical device shall comply with the requirements of this Directive and of the [revised Regulation (EC) No 726/2004] taking into account its use with the medical device, without prejudice to the specific requirements of the Regulation (EU) 2017/745 **and of the Regulation (EU) 2017/746** [15]**, as applicable**.

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[14] 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).

[15] **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. 176–332)**

(86) For all these products (integral combinations of a medicinal product and a medical device **or in vitro diagnostic**, medicinal products in exclusive use with medical devices and combinations of a medicinal product with a product other than a medical device) the competent authority 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 product in exclusive use with a medical device that is not ancillary to that of the medical device, the marketing authorisation applicant shall also, upon request from the competent authority, submit any additional information related to the 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 the [revised Regulation (EC) No 726/2004].

(87) For integral combination 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 product in terms of compliance of the medicinal product with the requirements of this Directive and the [revised Regulation(EC) No 726/2004] and should ensure coordination of the information flow between the sectors throughout the assessment procedure and the lifecycle of the medicinal product.

(92) In order to increase the preparedness and responsiveness against health threats, in particular the emergence of antimicrobial resistance, adapted frameworks may be relevant to facilitate the rapid change of antimicrobials composition to maintain their efficacy. The use of established platforms would allow efficient and timely adaptation of those medicinal products to the clinical context.

(93) To optimise the use of resources for both applicants for marketing authorisation and competent authorities and avoid duplication of assessment 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 Pharmacopeia, instead of submitting the relevant data as required in accordance with Annex II. An active substance master file certificate may be granted by the Agency when the relevant data on the active substance concerned is not already covered by a monograph of the European Pharmacopeia or by another active substance master file certificate. **Where a certificate of suitability to the monographs of the European Pharmacopoeia or an active substance master file certificate is used as part of the marketing authorisation application, there may be a need 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 use 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 case of novel excipients, adjuvants, radiopharmaceutical precursors and active substance intermediates, when the intermediate is a chemical active substance by itself or used in conjugation with a biological substance.

(97) Access to individual patient data from clinical studies in structured format allowing for statistical analyses **can** ~~is valuable to~~ assist regulators in understanding the submitted evidence and to inform regulatory decision-making on the benefit-risk balance of a medicinal product. The introduction of such 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 Regulation (EU) 2016/679[16] and Regulation (EU) 2018/1725[17] of the European Parliament and of the Council.

(104) 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[18], and restricted to those authorised in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives[19], for which specifications are laid down in Commission Regulation (EU) No 231/2012[20]. Uses of excipients other than colours in medicinal products are subject to the Union rules on medicinal products and are evaluated as part of the overall benefit risk profile of a medicinal product.

16 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).

17 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).

18 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).

19 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).

20 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).

(105) 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 foresee a specific assessment for the use of the colour in medicines when a food additive is removed from Union list of food additives. Therefore, in this specific case, EMA should carry out its own assessment for the use of the colour in medicines, taking into account the EFSA opinion and its underlying scientific evidence, as well as any additional scientific evidence and giving particular consideration to the use in medicines. EMA 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.

(111) 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 have the power 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 and rely on the outcome of inspections conducted by trusted third countries competent authorities. To preserve the effectiveness of the inspections, the competent authorities should have the possibility to perform joint inspections and also, where necessary, unannounced inspections.

REVISED REGULATION

(43) In the interest of public health, marketing authorisation decisions under the centralised procedure should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations. However, Member States should be able, exceptionally, to prohibit the use in their territory of medicinal products for human use.

(44) The quality, safety and efficacy criteria of [revised Directive 2001/83/EC] should apply to medicinal products authorised by the Union under the centralised procedure. The benefit-risk balance of all medicinal products will be assessed when they are placed on the market, and at any other time the competent authority deems appropriate.

(45) Marketing authorisation applications, like any other application submitted to the Agency, should follow the digital by default principle and hence be sent to the Agency in electronic form. Applications should be assessed based on the file submitted by the applicant in accordance with the different legal basis provided by [revised Directive 2001/83/EC]. At the same time, the Agency and the relevant committees may take into account any information that is in its possession. Applicants shall be requested to generally submit raw data, in particular with regard to the clinical trials performed by the applicant in order to ensure a full assessment of the quality, safety and efficacy of the medicinal product.

(46) Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes[21] lays down provisions on the protection of animals used for scientific purposes based on the principles of replacement, reduction and refinement. Any study involving the use of live animals, which provides essential information on the quality, safety and efficacy of a medicinal product, should take into account those principles of replacement, reduction and refinement, where they concern the care and use of live animals for scientific purposes, and should 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 Agency and the International Committee for Harmonisation (ICH) guidelines. In particular, the marketing authorisation applicant and the marketing authorisation holder should take into account the principles laid down in Directive 2010/63/EU, including, where possible, use of new approach methodologies in place of animal testing. These can include but are not limited to: in vitro models, such as microphysiological systems including organ-on-chips, (2D and 3D) cell culture models, organoids and human stem cells-based models; in silico tools or read-across models.

[21] 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).

(47) Procedures should be in place to facilitate joint animal testing, wherever possible, in order to avoid unnecessary duplication of testing using live animals covered by 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.

(48) The summary of product characteristics and the package leaflet should reflect the assessment of the Agency and be part of its scientific opinion. The opinion may recommend certain conditions that should be part of the marketing authorisation, for example on the safe and efficacious use of the medicinal product or on post-authorisation obligations that have to be complied with by the marketing authorisation holder. Those conditions may include the requirement to conduct post-authorisation safety or efficacy studies or other studies that are considered necessary to optimise the treatment, for example where the proposed dose scheme by the applicant, whilst acceptable and justifying a positive benefit-risk balance, could be further optimised post-authorisation. Where the applicant disagrees with parts of the opinion, the applicant may request its re-examination.

(49) Due to the need to reduce overall approval times for medicinal products, the time between the opinion of the Committee for Medicinal Products for Human Use (CHMP) and the final decision on the application for a marketing authorisation should in principle be no longer than 46 days.

(50) On the basis of the opinion of the Agency the Commission should adopt a decision on the application by means of implementing acts. In justified cases, the Commission may return the opinion for further examination or deviate in its decision from the opinion of the Agency. 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 will use the available mechanisms under Regulation (EU) 182/2011 of the European Parliament and of the Council[22] and notably the possibility to obtain the committee's opinion by written procedure and within expeditious deadlines which, in principle, will not exceed 10 calendar days.

(51) As a general rule a marketing authorisation should be granted for an unlimited time; however, one renewal may be decided only on justified grounds related to the safety of the medicinal product.

(52) There is a need to provide for the ethical requirements of Regulation (EU) No 536/2014 to apply to medicinal products authorised by the Union. In particular, with respect to clinical trials conducted outside the Union on medicinal products destined to be authorised within the Union, at the time of the evaluation of the application for authorisation, it should be verified that these trials were conducted in accordance with the principles equivalent to these of Regulation (EU) No 536/2014 as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial.

[22] 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).

(53) Environmental risks may arise from medicinal products containing or consisting of genetically modified organisms. It is thus necessary to subject such medicinal products to an environmental risk-assessment procedure similar to the procedure under Directive 2001/18/EC of the European Parliament and of the Council[23], to be conducted in parallel with the evaluation, under a single Union procedure, of the quality, safety and efficacy of the medicinal product concerned. The environmental risk-assessment should be conducted in accordance with the requirements set out in this Regulation and in [revised Directive 2001/83/EC] which are based on the principles set out in Directive 2001/18/EC but taking into account the specificities of medicinal products.

(54) [revised Directive 2001/83/EC] permits Member States to temporarily allow the use and supply of unauthorised medicinal products for public health reasons or individual patient needs and that includes medicinal products to be authorised under this Regulation. It is also necessary, that Member States are allowed under this Regulation to make a medicinal product available for compassionate use prior to its marketing authorisation. In those exceptional and urgent situations, where there is a lack of a suitable authorised medicinal product, the need to protect public health or the health of individual patients must prevail over other considerations, in particular the need to obtain a marketing authorisation and consequently, to have available complete information about the risks posed by the medicinal product, including any risks to the environment from medicinal products containing or consisting of genetically modified organisms (GMOs). To avoid delays in making these products available or uncertainties as regards their status in certain Member States, it is appropriate, in those exceptional and urgent situations, that for a medicinal product containing or consisting of GMOs, an environmental risk assessment or consent in accordance with Directive 2001/18/EC or Directive 2009/41/EC of the European Parliament and of the Council[24] should not be a prerequisite. Nevertheless, in these cases, Member States should implement appropriate measures to minimise foreseeable negative environmental impacts resulting from the intended or unintended release of the medicinal products containing or consisting of GMOs into the environment.

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23 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).

24 Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (Recast) (OJ L 125, 21.5.2009, p. 75).

(55) For medicinal products, the period for protection of data relating to non-clinical tests and clinical trials should be the same as that provided for in [revised Directive 2001/83/EC].

(56) In order to meet, in particular, the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies, accelerated assessment procedures should be set up, reserved for medicinal products of major therapeutic interest, and procedures for obtaining conditional marketing authorisations subject to certain regularly reviewable conditions.

(57) Compassionate use programmes allow for an early access to medicinal products. Existing provisions should be reinforced to ensure that a common approach is followed, whenever possible, regarding the criteria and conditions for the compassionate use of new medicinal products under Member States' legislation. Moreover, it is important to allow for data on such uses to be collected to inform decisions regarding the benefit-risk balance of the medicinal products concerned.

(58) 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. The legislation should allow under similar circumstances for medicinal products with a standard marketing authorisation for new indications to be authorised on a conditional basis or under exceptional 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 shall be subject to specific review of the fulfilment of the imposed specific conditions or obligations. It is also understood that the grounds for refusal of a marketing authorisation shall apply *mutatis mutandis* for such cases.

(59) In principle, only one marketing authorisation may be granted to an applicant for a medicinal product. Duplicate marketing authorisations should only be granted in exceptional circumstances. When those exceptional circumstances are no longer present, notably as regards the protection by a patent or a supplementary protection certificate in one or more Member States, any potentially negative effects on markets from the existence of duplicate marketing authorisations should be minimised through a withdrawal of the initial or the duplicate marketing authorisation.

(60) Regulatory decision-making on the development, authorisation and supervision of medicinal products may be supported by access and analysis of health data, including real world data, where appropriate, i.e. health data generated outside of clinical studies. The Agency should be able to use such data, including via the Data Analysis and Real World Interrogation Network (DARWIN) and the European Health Data Space interoperable infrastructure. Through these capabilities the Agency may take advantage of all the potential of supercomputing, artificial intelligence and big data science to fulfil its mandate, without compromising privacy rights. Where necessary the Agency may cooperate with the competent authorities of the Member States towards this objective.

(61) The handling of health data requires a high level of protection against cyber attacks. It is necessary for the Agency to be equipped with a high level of security controls and processes against cyber attacks to ensure that the Agency operates normally at all times. To that end, the Agency should establish a plan to prevent, detect, mitigate and respond to cyber attacks so that its operations are secure at all times, while preventing any illegal access to documentation held by the Agency.

(62) Due to the sensitive nature of health data, the Agency 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 Regulation, such processing should be done in accordance with Union law on the protection of personal data. Any processing of personal data under this Regulation should take place in accordance with Regulation (EU) 2016/679[25] and Regulation (EU) 2018/1725[26] of the European Parliament and of the Council.

(63) Access to individual patient data from clinical studies in structured format allowing for statistical analyses **can be** ~~is~~ valuable to assist regulators in understanding the submitted evidence and to inform regulatory decision-making on the benefit-risk balance of a medicinal product. The introduction of such possibility in the legislation is important to foster data-driven benefit-risk assessments at all stages of the life cycle of a medicinal product. This Regulation therefore empowers the Agency to request such data as part of the assessment of initial and post-authorisation applications.

(64) For generic and biosimilar medicinal products, as a general rule, risk management plans should not be developed and submitted, also considering that the reference medicinal product has such a plan; however, in specific cases, a risk management plan for generic and biosimilar medicinal products should be developed and submitted to the competent authorities.

(65) In the preparation of scientific advice and in duly justified cases, the Agency should also be able to consult authorities established in other relevant Union legal acts or other public bodies established in the Union, as applicable. These may include experts in clinical trials, medical devices, substances of human origin or any other as required for the provision of the scientific advice in question.

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[25] 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).

[26] 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).

(66) Through the Priority Medicines (PRIME) scheme, the Agency has gained experience of the provision of early scientific and regulatory support to developers of certain medicinal products that, based on preliminary evidence, are likely to address an unmet medical need and are considered promising at an early stage of development. It is appropriate to recognise this early support mechanism, including for priority antimicrobials and repurposed medicinal products when they fulfil the criteria for the scheme, and allow the Agency, in consultation with the Member States and the Commission, to establish selection criteria for promising medicinal products.

(67) The Agency, in consultation with the Member States and the Commission, should set the scientific selection criteria for medicinal products that receive pre-authorisation support with priority to be given to the most promising developments in therapies. In the case of medicinal products for unmet medical needs, based on the scientific selection criteria set by the Agency, any interested developer can submit preliminary evidence to demonstrate that the medicinal product has the potential to provide a major therapeutic advancement with respect to the identified unmet medical need.

(68) Before a medicinal product for human use is authorised for placing on the market of one or more Member States, it generally has to undergo extensive studies to ensure that it is safe, of high quality and effective for use in the target population. However, in the case of certain categories of medicinal products for human use, in order to meet unmet medical needs of patients and in the interest of public health, it may be necessary to grant marketing authorisation on the basis of less complete data than is normally the case. Such marketing authorisation should be granted subject to specific obligations. The categories of medicinal products for human use concerned should be the medicinal products, ~~including orphan medicinal products,~~ that aim at the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, or that are intended to be used in emergency situations in response to public health threats.

(69) The Union should have the means to carry out a scientific assessment of the medicinal products presented in accordance with the decentralised marketing authorisation procedures. Moreover, with a view to ensuring the effective harmonisation of administrative decisions taken by Member States with regard to medicinal products presented in accordance with decentralised marketing authorisation procedures, it is necessary to endow the Union with the means to resolve disagreements between Member States concerning the quality, safety and efficacy of medicinal products.

(70) In the event of a risk to public health, the marketing authorisation holder or the competent authorities should be able to make urgent safety or efficacy restrictions on their own initiative to ensure a swift adaption of the marketing authorisation to maintain the safe and efficacious use of the medicinal product by healthcare professionals and patients. If a review is launched on the same safety or efficacy concern addressed by urgent restrictions initiated by a competent authority, any written observations by the marketing authorisation holder should be considered in that review to avoid duplication of assessment.

(71) The terms of a marketing authorisation for a medicinal product for human use may be varied. While the core elements of a variation are laid down in this Regulation, the Commission should be empowered to complement these elements by laying down further necessary elements, to adapt the system to technical and scientific progress, and to employ digitalisation measures to ensure that unnecessary administrative burden is avoided for marketing authorisation holders and competent authorities.

(72) To avoid unnecessary administrative and financial burden both for the pharmaceutical industry and the competent authorities, certain streamlining measures should be introduced. Electronic applications for marketing authorisations and for variations to the terms of the marketing authorisation should be made possible.

(73) To optimise the use of resources for both applicants for marketing authorisations and competent authorities assessing such applications, a single assessment of an active substance master file should be introduced. The outcome of the assessment should be issued through a certificate. To avoid duplication of assessment, the use of an active substance master file certificate should be mandatory for subsequent applications or marketing authorisations for medicinal products for human use containing that active substance from an active substance master file certification holder. 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 extend the certification scheme to additional quality master files, e.g. in case of novel excipients, adjuvants, radiopharmaceutical precursors and active substance intermediates, when the intermediate is a chemical active substance by itself or used in conjugation with a biological substance.

(74) To avoid unnecessary administrative and financial burdens for applicants, marketing authorisation holders and competent authorities, certain streamlining measures should be introduced. Electronic application for marketing authorisation and for variations to the terms of the marketing authorisation should be introduced. For generic and biosimilar medicinal products, except in specific cases, risk management plans do not need to be developed and submitted to the competent authorities.

REVISED DIRECTIVE

Chapter II
Application requirements for national and centralised marketing authorisations

Section 1
General provisions

Article 5
Marketing authorisations

1. A medicinal product shall be placed on the market of a Member State only when a marketing authorisation has been granted by the competent authorities of a Member State in accordance with Chapter III ('national marketing authorisation') or a marketing authorisation has been granted in accordance with [revised Regulation (EC) No 726/2004] ('centralised marketing authorisation').

2. When an initial marketing authorisation has been granted in accordance with paragraph 1, any development concerning the medicinal product covered by the authorisation such as additional therapeutic indication, strengths, pharmaceutical forms, administration routes, presentations, as well as any variations of the marketing authorisation shall also be granted an authorisation in accordance with paragraph 1 or be included in the initial marketing authorisation. All those marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the marketing authorisations applications under Articles 9 to 12, including as regards the expiry of the regulatory data protection period for applications using a reference medicinal product.

Article 6

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 concerned in a common format. The Agency shall make available such format after consultation with the Member States.

2. The marketing authorisation application shall include the particulars and documentation listed in Annex I, submitted in accordance 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 7 and**, when requested by the competent authority,** ~~supportive~~ raw data.

3a. Where a marketing authorisation is withdrawn, but medicinal product previously placed on the market under that marketing authorisation remains to be made available on the market, all relevant obligations and post-marketing provisions of this Directive and of [revised Regulation 726/2004/EC] shall continue to apply as appropriate until such time as all remaining stock of the medicinal product has expired.

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 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 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate, shall include one of the following:

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

(b) a decision of the Agency granting a product-specific waiver pursuant to Article 75(1) of [revised Regulation No (EC) 726/2004];

(c) a decision of the Agency granting a class waiver pursuant to Article 75(2) of [revised Regulation No (EC) 726/2004];

(d) a decision of the Agency granting a deferral pursuant to Article 81 of [revised Regulation No (EC) 726/2004];

(e) a decision of the Agency taken in consultation with the Commission pursuant to Article 83 of [revised Regulation No (EC) 726/2004] to temporarily derogate from the provision referred to in points (a) to (d) above in case of health emergencies.

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

6. The provisions of paragraph 5 shall not apply to medicinal products authorised under Articles 9, 11, 13, Articles 125 to 141 and medicinal products authorised under Articles 10 and 12 which are not protected either by a supplementary protection certificate under [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate.

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

The marketing authorisation applicant shall not carry out animal testing in case scientifically satisfactory non-animal testing methods are available.

Article 7

Expert verification

1. The marketing authorisation applicant shall ensure that the detailed summaries referred to in Article 6(3) have been drawn up and signed by experts with the necessary technical or professional qualifications before they are submitted to the competent authorities. 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 shall justify any use made of scientific literature under Article 13 in accordance with the requirements set out in Annex II.

Article 8

Medicinal products manufactured outside the Union

Member States shall take all appropriate measures to ensure that:

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

(b) the competent authorities ~~of the Member States~~ 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 ~~of the Member States~~ shall also be made in the establishment designated.

Section 2

Specific requirements for abridged, bibliographic or consent based applications for marketing authorisation

Article 9

Applications concerning generic medicinal products

1. By way of derogation from Article 6(2), the applicant for a marketing authorisation for a generic medicinal product shall not be required to provide to the competent authorities the results of non-clinical tests and of clinical studies if ~~**therapeutic**~~ equivalence of the generic medicinal product with the reference medicinal product is demonstrated.

2. For the purpose of demonstrating the equivalence as referred to in paragraph 1, the applicant shall submit to the competent authorities equivalence studies, or a justification as to why such studies were not performed, and demonstrate that the generic medicinal product meets the relevant criteria set out in the appropriate detailed guidelines.

3. Paragraph 1 shall also apply if the reference medicinal product has not been authorised in the Member State in which the application for the generic medicinal product is submitted. In this case, the applicant shall indicate in the application 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 application 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. In those cases, the applicant 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 prove 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 an application under Article 10.

Article 10

Applications concerning hybrid medicinal products

In cases where the medicinal product does not fall within the definition of a generic medicinal product or has changes in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference medicinal product, the results of the appropriate non-clinical tests or clinical studies shall be provided to the competent authorities 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 11

Applications concerning biosimilar medicinal products

For a biological medicinal product that is similar to a reference biological medicinal product (‘biosimilar medicinal product’), the results of appropriate comparability tests and studies shall be provided to the competent authorities. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated 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 provided.

Article 12

Applications concerning bio-hybrid medicinal products

In cases where ~~a biosimilar~~**the biological** medicinal product **does not fall within the definition of a biosimilar medicinal product or** has changes in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference biological medicinal product ('bio-hybrid'), the results of the appropriate non-clinical tests or clinical studies shall be provided to the competent authorities 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 ~~or~~ **and** efficacy profile of the ~~biosimilar~~ **bio-hybrid** medicinal product.

Article 13

Applications based on bibliographic data

In cases where**, at the time of submission of the marketing authorisation application, no** ~~no~~ reference medicinal product is or has been authorised **or if a reference medicinal product has been authorised but is not available on the market within the Union** for the active substance of the medicinal product concerned, the applicant shall, by way of derogation from Article 6(2), not be required to provide the results of non-clinical tests or clinical studies if the 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 and 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 that event, the test and trial results shall be replaced by appropriate bibliographic data in the form of scientific literature**, and the applicant shall establish** ~~**together with the data establishing a**~~ **scientific bridge between the bibliographic data and the medicinal product concerned**.

Article 14

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 6(2) ~~with a view to~~ **for the purpose of** examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

Section 3
Specific requirements for applications for certain categories of medicinal products

Article 15

*Fixed dose combination medicinal product, platform ~~technologies~~ **marketing authorisations** and multi-medicinal product packages*

1. Where justified for ~~therapeutic~~ **medical clinical** purposes, a marketing authorisation may be granted for a fixed dose combination medicinal product.

2. Where justified for ~~therapeutic~~ **clinical** purposes **~~public health reasons~~**, a marketing authorisation may~~, in exceptional circumstances,~~ 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 technology')~~ **(platform marketing authorisation)**.

   An applicant that intends to submit an application for a marketing authorisation for such a medicinal product shall seek, in advance, the agreement concerning the submission of such application by the competent authority concerned.

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

An applicant that intends to submit ~~a~~ an application for a marketing authorisation for such a medicinal product shall seek, in advance, the agreement concerning the submission of such application by the competent authority concerned.

Article 16

Radiopharmaceuticals

1. A marketing authorisation shall be required for radionuclide generators, kits **for radiopharmaceutical preparation**, and radionuclide precursors, unless they are used as starting material, active substance or intermediate of radiopharmaceuticals covered by a marketing authorisation under Article 5(1).

2. A marketing authorisation shall not be required for a radiopharmaceutical prepared at the time of use by a person or by an establishment authorised, according to national legislation, to use such radiopharmaceutical in an approved healthcare establishment exclusively from authorised radionuclide generators, kits **for radiopharmaceutical preparation** or radionuclide precursors in accordance with the ~~authorised~~ manufacturer's instructions **in the authorised product information**.

Article 17

Antimicrobials

1. Where the application for a marketing authorisation concerns an antimicrobial, the application shall, in addition to the information referred to in Article 6, contain the following:
   (a) an antimicrobial stewardship plan as referred to in Annex I;
   (b) a description of the special information requirements outlined in Article 69 and listed in Annex I.

2. The competent authority may impose obligations on the marketing authorisation holder if it finds the risk mitigation measures contained in the antimicrobial stewardship plan unsatisfactory.

3. The marketing authorisation holder shall ensure**, where the pack is intended for direct dispensing to patients,** that the pack size of the antimicrobial corresponds to the usual posology and duration of treatment.

Article 18

Integral combinations of medicinal products and medical devices

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

   As part of the assessment, in accordance with Article 29, of the integral combination of a medicinal product and a medical device the competent authorities shall assess the benefit-risk balance of the integral combination of a medicinal product and 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 of Regulation (EU) 2017/745 shall apply as far as the safety and performance of the medical device part of the integral combination of a medicinal product with a medical device are concerned.

3. The application for a marketing authorisation for an integral combination of a medicinal product with a medical device shall include the documentation supporting the compliance of the medical device part with the general safety and performance requirements as referred to in paragraph 2 in accordance with Annex II, including~~,~~ **the results of the conformity assessment of the device part with the general safety and performance requirements of Regulaton (EU) 2017/745 or an opinion on the conformity of the device part with the general safety and performance requirements of Regulation (EU) 2017/745 by a notified body**~~where relevant, the conformity assessment report by a notified body~~.

4. In its evaluation of the integral combination of a medicinal product with a medical device concerned, the competent authorities shall recognise the results of the assessment of compliance of the medical device part of that integral combination with the general safety and performance requirements in accordance with Annex I of Regulation (EU) 2017/745 including, where relevant, the results of the assessment by a notified body.

5. The marketing authorisation applicant shall, upon request from the competent authority, 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 referred to in paragraph 1.

Article 19

Medicinal products in exclusive use with medical devices ***or in-vitro diagnostic medical devices***

1. For medicinal products in exclusive use with a medical device the marketing authorisation applicant shall submit data establishing the safe and effective use of the medicinal product taking into account its use with the medical device.

   As part of the assessment, in accordance with Article 29, of the medicinal product referred to in the first subparagraph, the competent authorities shall assess the benefit-risk balance of the medicinal product taking into account the use of the medicinal product together with the medical device.

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

3. The application for a marketing authorisation for a medicinal product in exclusive use with a medical device shall include the documentation supporting the compliance of the medical device with the general safety and performance requirements ~~as referred to in paragraph 2~~ in accordance with Annex II, including, where relevant, **the results of** the ~~conformity~~ assessment **or the conformity assessment** report by a notified body.

4. In its evaluation of the medicinal product referred to in paragraph 1 the competent authority shall recognise the results of the assessment of compliance of the medical device concerned with the general safety and performance requirements in accordance with Annex I of Regulation (EU) 2017/745 **~~and~~ or (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 authority, submit any additional information related to the medical device and that is relevant for the benefit-risk balance assessment of the medicinal product referred to in paragraph 1, taking into account the use of the medicinal product with the medical device.

6. If the action of the medicinal product is not ancillary to that of the medical device, the medicinal product shall comply with the requirements of this Directive and of the [revised Regulation (EC) No 726/2004], taking into account its use with the medical device, without prejudice to the specific requirements of the Regulation (EU) 2017/745 **or (EU) 2017/746, as applicable**.

   In this case, the marketing authorisation applicant shall, upon request from the competent authorities, submit any additional information related to the 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 the [revised Regulation (EC) No 726/2004].

Article 20

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 establishing the safe and effective use of the combination of the medicinal product and the other product.

As part of the assessment, in accordance with Article 29, of the combination of a medicinal product with a product other than a medical device the competent authority shall assess the benefit-risk balance of the combination of a medicinal product and 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 submit any additional information related to the product other than medical devices and that is relevant for the benefit-risk balance assessment of the combination of medicinal products with the product other than medical devices, taking into account the suitability of the use of the medicinal product with the product referred to in paragraph 1.

3. The competent authority may request ~~for~~ an opinion ~~of~~ from the authority competent for the supervision of the product other than a medical device.

Section 4
Specific dossier requirements

Article 21
Risk management plan

1. The applicant of a marketing authorisation for a medicinal product referred to in Articles 9~~,~~ and 11 **~~and 14~~** 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 application.

2. **The risk management plan for ~~hybrid and bio-hybrid~~ a medicinal products referred to in Articles 10 and 12 shall ~~cover only the risk management system that is specific to the hybrid and bio-hybrid medicinal product~~ be limited to the differences between this medicinal product 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 application~~., as set indicated in the application for the marketing authorisation.~~**

Commented [A1]: SI: Minor editorial correction is suggested to be in line with the previous paragraph.

Article 22

Environmental risk assessment and other environmental information

1. When preparing the environmental risk assessment ('ERA') to be submitted pursuant to Article 6(2), the applicant shall take into account the scientific guidelines on the environmental risk assessment of medicinal products for human use as referred to in paragraph **5**~~6~~, or provide the reasons for any divergence from the scientific guidelines to the Agency or, as appropriate to the competent authority of the Member State concerned, in a timely manner. Where available, the applicant shall take into account existing ERAs performed under other Union legislation.

2. The ERA shall indicate whether the medicinal product or any of its ingredients or other constituents is one of the following substances according to the criteria of Annex I to the Regulation (EC) No 1272/2008:
   (a) persistent, bioaccumulative and toxic (PBT);
   (b) very persistent and very bioaccumulative (vPvB);
   (c) persistent, mobile and toxic (PMT), very persistent and very mobile (vPvM);
   or are endocrine **disrupting** ~~active agents~~ **disruptors**.

3. **Where the ERA identifies a risk to the environment,** ~~T~~the applicant shall also include in the ERA risk mitigation measures to avoid or where it is not possible, limit emissions to air, water and soil. Mitigation measures should also be taken for ~~of~~ **ingredients and constituents of medicinal products listed as** ~~of~~ pollutants ~~listed~~ in Directive 2000/60/EC, Directive 2006/118/EC, Directive 2008/105/EC and Directive 2010/75/EU. The applicant shall provide detailed explanation that the proposed mitigation measures are appropriate and sufficient to address the identified risks to the environment.

Commented [A2]: SI: It is unclear, therefore the amendment is proposed.

The ERA might identify risk of other substances, not only the ones listed as pollutants.

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 of the antimicrobial taking into account, where relevant, the existing international standards that have established predicted no effect concentration (PNECs) specific for antibiotics.

5. The Agency shall draw up scientific guidelines in accordance with Article 138 of [revised Regulation No (EC) 726/2004], to specify technical details regarding the ERA requirements for medicinal products for human use. Where appropriate, the Agency shall consult the European Chemical Agency (ECHA), the European Food Safety Authority (EFSA) and the European Environmental Agency (EEA) on the drafting of these scientific guidelines.

6. The marketing authorisation holder shall update the ERA with new information without undue delay to the relevant competent authorities, in accordance with Article 90(2), if new information pertaining to the assessment criteria referred to in Article 29 becomes available and could lead to a change of the conclusions of the ERA. The update 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 legislation, as referred to in paragraph 1, and environmental exposure data.

~~For an ERA conducted prior to [OP please insert the date = 18 months after the date of entering into force of this Directive], the competent authority shall request the marketing authorisation holder to update the ERA if missing information has been identified for medicinal products potentially harmful to the environment.~~

7. For medicinal products referred to in Articles 9 to 12 **and 14 and fixed-dose combinations ~~of established active substances~~**, the applicant may refer to ERA studies conducted for the reference medicinal product **or to ERA studies of any other medicinal product containing the same active substances~~(s),~~** when preparing the ERA.

Article 23

ERA of medicinal products authorised before 30 October 2005

1. By [OP please insert the date = 30 months after the date of the entry into force of this Directive] the Agency shall, after consultation with the competent authorities of the Member States, the European Chemical Agency (ECHA), the European Food Safety Authority (EFSA) and the European Environmental Agency (EEA), establish a programme for the ERA to be submitted in accordance with Article 22 of the medicinal products authorised before 30 October 2005 that have not been subject to any ERA and that the Agency has identified as potentially harmful to the environment in accordance with paragraph 2.

   This programme shall be made publicly available by the Agency.

2. The Agency shall set the scientific criteria for the identification of the medicinal products as potentially harmful to the environment and for the prioritisation of their ERA, using a risk based approach. For this task, the Agency may request from marketing authorisation holders the submission of relevant data or information.

3. The marketing authorisation holders for medicinal products identified in the programme referred to in paragraph 1 shall submit the ERA to the Agency. The outcome of the assessment of the ERA including the data submitted by the marketing authorisation holder shall be made publicly available by the Agency.

4. Where there are several medicinal products identified in 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 authorities of the Member States or the Agency shall encourage the marketing authorisation holders to conduct joint studies for the ERA, to minimise unnecessary duplication of data and use of animals.

5. **For medicinal products referred to in Articles 9 to 12 and 14 and fixed-dose combinations ~~of established active substances~~, for which the reference medicinal product has been authorised before 30 October 2005, and which are included in this programme, the ERA shall be submitted after the outcome of the ERA of such reference medicinal product is made publicly available by the Agency.**

Article 24

System of ERA monographs of the ERA data of active substances

1. The Agency shall, in collaboration with the competent authorities of the Member States, set-up an active substance based review system of ERA data ('ERA monographs') for authorised medicinal products. An ERA monograph shall include a comprehensive set of physiochemical data, fate data and effect data based on an assessment of a competent authority.

2. The setting-up of the system of ERA monographs shall be based on a risk-based prioritisation of active substances.

3. In the preparation of the ERA monograph referred to in paragraph 1, the Agency may request ~~existing~~ **available** information, studies and data from competent authorities of the Member States and from marketing authorisation holders.

4. The Agency in cooperation with the competent authorities of the Member States shall conduct a proof-of-concept pilot of ERA monographs to be completed within three years after entering into force of this Directive.

5. The Commission is empowered to adopt delegated acts in accordance with Article 215 and based on the results of a proof-of-concept pilot referred to in paragraph 4, 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 prioritisation criteria for the selection and prioritisation referred to in paragraph 2;
   (e) the use of ERA monographs in the context of new marketing authorisation applications for medicinal products to support their ERA.

Article 25

Active substance master file certificate

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 Pharmacopeia.

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

2. An active substance master file certificate may be granted by the Agency in cases where the relevant data on the active substance concerned is not already covered by a monograph of the European Pharmacopeia or by an active substance master file certificate.

In order to obtain an active substance master file certificate, an application 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 Pharmacopeia or an active substance master file certificate. The Agency shall examine the application and, in case of a positive outcome, shall grant the certificate that shall be valid throughout the Union. In 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 establish a repository of active substance master files, their assessments reports and their certificates and ensure that personal data **and information of a commercially confidential ~~sensitive information are~~ nature** is protected. The Agency shall ensure that the competent authorities of the Member State have access to this repository.

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

4. The active substance master file certificate holder shall be the manufacturer of the active substance.

5. The active substance master file certificate holder shall keep the active substance master file up to date with 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 substance for which an application for an active substance master file certificate has been submitted or the active substance master file certificate holder shall undergo an inspection to verify the information contained in the application or the active substance master file or their compliance with good manufacturing practices for active substances referred to in Article 160.

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

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

8. The marketing authorisation holder of the medicinal product 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 215 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 examination of an application for an active substance master file certificate and for the granting of the certificate;
   (c) the rules for making publicly available of active substance master file certificates;
   (d) the rules for introducing changes to the active substance master file and the active substance master file certificate;
   (e) the rules on access for competent authorities of the Member States to the active substance master file and its assessment report;
   (f) the rules on access for marketing authorisation applicants and marketing authorisation holders relying on an active substance master file certificate to the active substance master file and to the assessment report.

Article 26

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 Pharmacopeia.

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

2. Article 25, paragraphs 1 to 5, 7 and 8 shall also apply *mutadis mutandis* to additional quality master file certification.

2a. The Commission is empowered to adopt delegated acts to identify, 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.

3. The Commission is empowered to adopt delegated acts in accordance with Article 215 to supplement this Directive by specifying:
   (a) the rules governing the content and format of the application for an ~~active substance~~ **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 applications for making publicly available of additional quality master file certificates;
   (d) the rules for introducing changes to the additional quality master file and the certificate;

(e) the rules on access for competent authorities of the Member State to the additional quality master file and its assessment report;

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

4. 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 additional quality master file certificate holder shall undergo an inspection to verify the information contained in the application or the quality master file.

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

Article 27

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.

Excipients shall be examined by the competent authorities 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 in Part B of Annex II to Regulation (EC) No 1333/2008 and comply with the purity criteria and specifications laid down in Commission Regulation (EU) No 231/2012;

(b) the list 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 whether the colour concerned shall be added to list of colours permitted for use in medicinal products referred to in the first subparagraph.

A colour may be added to the list of colours permitted for use in medicinal products only where the colour has been removed from the Union list of authorised food additives.

Where relevant, the list of colours permitted for use in medicinal products shall include purity criteria, specifications or restrictions applicable to the colours included in that list.

The list of colours permitted for use in medicinal products shall be established by way of implementing acts. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 214(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 European Food Safety Authority ('EFSA'), the Agency shall, on the request of the Commission or on its own initiative, without undue delay issue a scientific opinion as regards the use of the colour concerned in medicinal product, taking into account the opinion of the EFSA if relevant. The opinion of the Agency shall be adopted by 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 in medicinal product 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 permitted for use in medicinal products referred to in paragraph 3.

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 permitted for use in medicinal products referred to in paragraph 3. The Commission may, in such cases, request the opinion from the Agency.

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

7. Paragraphs 2 to 6 shall also apply to colours used in veterinary medicinal products as defined in Article 4(1) of Regulation (EU) 2019/6 of the European Parliament and of the Council [27].

REVISED REGULATION

Chapter II
GENERAL PROVISIONS AND RULES ON APPLICATIONS

Section 1
Application for centralised marketing authorisations

Article 5

Submission of applications for marketing authorisations

1. The marketing authorisation holder for medicinal products covered by this Regulation shall be established in the Union. The marketing authorisation holder shall be responsible for the placing on the market of those medicinal products, whether done by that marketing authorisation holder or via one or more persons designated to that effect.

[27] 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.

2. An applicant shall agree with the Agency the submission date of an application for a marketing authorisation.

3. An applicant shall submit an application for a marketing authorisation electronically to the Agency and in the formats made available by the Agency.

4. The applicant shall be responsible for the accuracy **and completeness** of the information and documentation submitted with respect to its application.

5. Within 20 days of receipt of an application, the Agency shall check whether all the information and documentation required in accordance with Article 6 have been submitted, that the application does not contain critical deficiencies that may prevent the evaluation of the medicinal product and decide whether the application is valid.

6. Where the Agency considers that the application is incomplete, or contains critical deficiencies that may prevent the evaluation of the medicinal product, it shall inform the applicant accordingly and set a time limit for submitting the missing information and documentation. That time limit may be extended once by the Agency.

   Upon receipt of the responses from the applicant to the request to submit the missing information and documentation, the Agency will determine whether the application can be considered valid. Where the Agency refuses to validate an application, it shall notify the applicant and state the reasons for such refusal.

   If the applicant fails to provide the missing information and documentation within the time limit, the application shall be considered to have been withdrawn.

7. The Agency shall draw up scientific guidelines for the identification of critical deficiencies that may prevent the evaluation of a medicinal product, in consultation with the European Commission and the Member States.

Article 6

Centralised marketing authorisation application

1. Each application for a centralised marketing authorisation of a medicinal product for human use shall specifically and completely include the particulars and documentation as referred to in Chapter II of [revised Directive 2001/83/EC]. In the case of applications in accordance with Article 6(2), Article 10 and Article 12 of [revised Directive 2001/83/EC], this~~, when requested by the Agency,~~ shall include the electronic submission of raw data, in accordance with Annex II of that Directive.

   The documentation shall include a declaration to the effect that clinical trials carried out outside the Union meet the ethical requirements of Regulation (EU) No 536/2014. Those particulars and documentation shall take account of the unique, Union nature of the authorisation requested and, otherwise than in exceptional cases relating to the application of the law on trademarks pursuant to Regulation (EU) 2017/1001 of the European Parliament and of the Council[28], shall include the use of a single name for the medicinal product. The use of a single name does not exclude the use of additional qualifiers where necessary to identify different presentations of the medicinal product concerned.

~~2. For medicinal products that are likely to offer an exceptional therapeutic advancement in the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Union, **are intended to be used in relation to potential or declared public health emergency** the Agency may, following the advice of the Committee for Medicinal Products for Human Use regarding the maturity of the data related to the development, offer to the applicant a phased review of complete data packages for individual modules of particulars and documentation as referred to in paragraph 1.~~

[28] Regulation (EU) 2017/1001 of the European Parliament and of the Council of 14 June 2017 on the European Union trade mark (OJ L 154, 16.6.2017, p. 1).

~~The Agency may at any stage suspend or cancel the phased review, where the Committee for Medicinal Products for Human Use considers that the submitted data are not of sufficient maturity or where it is considered that the medicinal product **cannot be used in relation to potential or declared public health emergency**no longer fulfils an exceptional therapeutic advancement. The Agency shall inform the applicant accordingly.~~

3. A fee shall apply for a marketing authorisation application and shall be payable to the Agency for the examination of the application.

4. Where appropriate, the application may include an active substance master file certificate or an application for an active substance master file or any other quality master file certificate or application as referred to in Article**s** 25 **and 26** of [revised Directive 2001/83/EC].

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

   The marketing authorisation applicant shall not carry out animal tests in case scientifically satisfactory non-animal testing methods are available.

6. The Agency shall ensure that the opinion of the Committee for Medicinal Products for Human Use is given within ~~180~~ **210** days after receipt of a valid application. In the case of a medicinal product for human use containing or consisting of genetically modified organisms, the opinion of that Committee shall take into account the evaluation of the environmental risk assessment in accordance with Article 8.

   On the basis of a duly reasoned request, the Committee for Medicinal Products for Human Use may call for the duration of the analysis of the scientific data in the file concerning the application for marketing authorisation to be extended.

7. When an application is submitted for a marketing authorisation in respect of medicinal products for human use which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation, the applicant may request an accelerated assessment procedure. The same shall apply for products referred to in Article 60. The request shall be duly substantiated. **The justification for an accelerated assessment ~~must~~ shall be included in the European public assessment report set out in Article 16.**

   If the Committee for Medicinal Products for Human Use accepts the request, the time-limit laid down in Article 6(6), first subparagraph, shall be reduced to 150 days.

Article 7

Environmental risk assessment for medicinal products containing or consisting of genetically modified organisms

1. Without prejudice to Article 22 of [revised Directive 2001/83/EC], the marketing authorisation application of a medicinal product for human use containing or consisting of genetically modified organisms as defined in Article 2(2) of Directive 2001/18/EC shall be accompanied by an environmental risk assessment identifying and evaluating potential adverse effects of the genetically modified organisms on human health and the environment.

2. The environmental risk assessment for the medicinal products referred to in paragraph 1 shall be conducted in accordance with the elements described in Article 8 and the specific requirements set out in Annex II to [revised Directive 2001/83/EC] based on the principles set out in Annex II to Directive 2001/18/EC taking into account the specificities of medicinal products.

3. Articles 13 to 24 of Directive 2001/18/EC **and Directive 2009/41/EC** shall not apply to medicinal products for human use containing or consisting of genetically modified organisms.

4. Articles 6 to 11 of [revised Directive 2001/18/EC] as well as Articles 4 to 13 of Directive 2009/41/EC shall not apply to operations related to the supply and clinical use, including the packaging and labelling, distribution, storage, transport, preparation for administration, administration, destruction or disposal of medicinal products containing or consisting of genetically modified organisms, with the exception of their manufacture, in any of the following cases:
   (a) where such medicinal products have been excluded from the provisions of [revised Directive 2001/83/EC] by a Member State pursuant to Article 3(1) of that Directive;
   (b) where the use and distribution of such medicinal products have been temporarily authorised by a Member State pursuant to Article 3(2) of [revised Directive 2001/83/EC]; or
   (c) where such medicinal products are made available by a Member State pursuant to Article 26(1).

5. In the cases referred to in paragraph 4, Member States shall implement appropriate measures to minimise foreseeable negative environmental impacts resulting from the intended or unintended release of the medicinal products containing or consisting of genetically modified organisms into the environment.

   The competent authorities of the Member States shall ensure that information related to the use of medicinal products referred to in paragraph 4, is available and provided to the competent authorities established by Directive 2009/41/EC, when necessary and in particular in the event of an accident referred to in Article 14 and Article 15 of Directive 2009/41/EC.

Article 8

Content of the environmental risk assessment for medicinal products containing or consisting of genetically modified organisms

The environmental risk assessment referred to in Article 7(2) shall contain the following elements:

(a) description of the genetically modified organism and the modifications introduced as well as characterisation of the finished product;

(b) identification and characterisation of hazards for the environment, animals and for human health;

(c) exposure characterisation, assessing the likelihood or probability that the identified hazards materialise;

(d) risk characterisation taking into account the magnitude of each possible hazard and the likelihood or probability of that adverse effect occurring;

(e) risk minimisation strategies proposed to address identified risks including specific containment measures to limit ~~**to prevent**~~ **dissemination of the medicinal product in the environment, that is not originating from the use inherent in human application** ~~contact with the medicinal product.~~**;**

(f) overall risk evaluation and conclusions.

Article 9

Procedure for the environmental risk assessment for medicinal products containing or consisting of genetically modified organisms

1. The applicant shall submit an environmental risk assessment referred to in Article 7(1) to the Agency.

   The Committee for Medicinal Products for Human Use shall assess the environmental risk assessment.

2. In case of first-in-class medicinal products or when a novel question is raised during the assessment of the submitted environmental risk assessment, the Committee for Medicinal Products for Human Use, or the rapporteur, shall **~~may~~, as necessary,** carry out ~~necessary~~ consultations with bodies Member States have set up in accordance with Directive 2001/18/EC. They may also consult with relevant Union bodies. Details on the consultation procedure shall be published by the Agency at the latest by [OJ:12 months after the date of entry into force of this Regulation].

Article 10

Committee assessment of an application for marketing authorisation

1. When preparing its opinion, the Committee for Medicinal Products for Human Use shall verify that the particulars and documentation submitted in accordance with Article 6 comply with the requirements of [revised Directive 2001/83/EC], and shall examine whether the conditions specified in this Regulation for granting a marketing authorisation are satisfied. When preparing its opinion, the Committee for Medicinal Products for Human Use may make the following requests:
   (a) that an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose tests the medicinal product for human use, its starting materials, ingredients and, where necessary, its intermediate products or other constituents in order to ensure that the control methods employed by the manufacturer and described in the application documents are satisfactory;
   (b) that the applicant supplements the particulars accompanying the application within a specific time period. In case of such a request, the time-limit set out in Article 6(6), first subparagraph, shall be suspended until the supplementary information requested is provided. Likewise, this time-limit shall be suspended for the time allowed for the applicant to prepare oral or written explanations.

2. Where within 90 days of the **date of** validation of the marketing authorisation application and during the assessment the Committee for Medicinal Products for Human Use considers that the submitted data are not of sufficient quality or maturity to complete the assessment, the assessment can be terminated ~~**suspended**~~. **Prior to the ~~end of the 90-day period~~ termination.** ~~T~~**t**he Committee for Medicinal Products for Human Use shall summarise the deficiencies in writing. On this basis, the Agency shall inform the applicant accordingly and set a time limit to address the deficiencies. The application shall be suspended until the applicant addresses the deficiencies. If the applicant fails to address those deficiencies within the time limit set by the Agency, **the ~~assessment~~ examination shall be terminated and** the application shall be considered as withdrawn.

Article 11

Certification of manufacturer

1. Upon receipt of a written request from the Committee for Medicinal Products for Human Use, a Member State shall forward the information demonstrating that the manufacturer of a medicinal product or the importer from a third country is able to manufacture the medicinal product concerned or carry out the necessary control tests, or both in accordance with the particulars and documents supplied by the applicant pursuant to Article 6.

2. The Committee for Medicinal Products for Human Use may, if it considers it necessary in order to complete the assessment, require the applicant to undergo a specific inspection of the manufacturing site of the medicinal product concerned.

   The inspection shall be carried out within the time-limit set out in Article 6(6), first subparagraph, by inspectors from the Member State holding the appropriate qualifications. Those inspectors may be accompanied by a rapporteur or an expert appointed by the Committee, or by one or more inspectors of the Agency. The inspections may be carried out unannounced.

   For manufacturing sites located in third countries, the inspection may be carried out by the Agency, following a request by the Member States and based on the procedure set out in Article 52.

Article 12

Committee Opinion

1. The Agency shall without undue delay inform the applicant if the opinion of the Committee for Medicinal Products for Human Use is that:
   (a) the application does not satisfy the criteria for marketing authorisation set out in this Regulation;
   (b) the application satisfies the criteria set out in this Regulation subject to changes required by the Agency to the summary of product characteristics are made;
   (c) the application satisfies the criteria set out in this Regulation provided that changes required by the Agency, to the labelling or package leaflet of the medicinal product, are made to ensure compliance with Chapter VI of [revised Directive 2001/83/EC];
   (d) where applicable, the application satisfies the criteria set out in Articles 18 and 19 subject to specific conditions therein.

2. Within 12 days of receipt of the opinion referred to in paragraph 1, the applicant may request by written notice to the Agency a re-examination of the opinion. In that case, the applicant shall provide the Agency with the detailed grounds for the request within 60 days after receipt of the opinion.

   The re-examination procedure may deal only with the points of the opinion initially identified by the applicant and may be based only on the scientific data available when the Committee for Medicinal Products for Human Use adopted the initial opinion.

   Within 60 days following receipt of the grounds for the request, the Committee for Medicinal Products for Human Use shall re-examine its opinion. The reasons for the conclusion reached shall be annexed to the final opinion.

3. Within 12 days after its adoption, the Agency shall send the final opinion of the Committee for Medicinal Products for Human Use to the Commission, to the Member States and to the applicant, together with a report describing the assessment of the medicinal product by the Committee for Medicinal Products for Human Use and stating the reasons for its conclusions.

4. If an opinion is favourable to the granting of the relevant marketing authorisation, the following**s** ~~documents~~ shall be annexed to the opinion:
   (a) a summary of product characteristics referred to in Article 62 of [revised Directive 2001/83/EC] and corresponding to the assessment of the medicinal product;
   (b) a recommendation on the frequency of submission of periodic safety update reports;
   (c) details of any conditions or restrictions to be imposed on the supply or use of the medicinal product concerned, including the conditions under which the medicinal product may be made available to patients, in accordance with the criteria laid down in Chapter XII of [revised Directive 2001/83/EC];
   (d) details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product;
   (e) details of any recommended measures for ensuring the safe use of the medicinal product to be included in the risk management system;
   (f) where appropriate, details of any recommended obligation to conduct post-authorisation safety studies or to comply with obligations on the recording or reporting of suspected adverse reactions which are stricter than those referred to in Chapter VIII;
   (g) where appropriate, details of any recommended obligation 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. Such an obligation to conduct such studies shall be based on the delegated acts adopted pursuant to Article 21 while taking into account the scientific guidance referred to in Article 123 of [revised Directive 2001/83/EC];
   (h) where appropriate, details of any recommended obligation to conduct any other post-authorisation studies to improve the safe and effective use of the medicinal product;
   (i) in case of medicinal products for which there is ~~substantial~~ **specific** uncertainty as to the surrogate endpoint relation to the expected health outcome, where appropriate and relevant for the benefit-risk balance, **details of any** ~~**a request for** a~~ post-authorisation obligation to substantiate the clinical benefit;
   (j) where appropriate, details of any recommended obligation to conduct additional post-authorisation environmental risk assessment studies, collection of monitoring data or information on use, where concerns about risks to the environment or public health, including antimicrobial resistance need to be further investigated after the medicinal product has been marketed;

(k) the text of the labelling and package leaflet, presented in accordance with Chapter VI of [revised Directive 2001/83/EC];

(l) the assessment report as regards the results of the pharmaceutical and non-clinical tests and of the clinical trials, and as regards the risk management system and the pharmacovigilance system for the medicinal product concerned;

(m) where appropriate, ~~to carry~~ **~~the results of~~** ~~out~~ **~~a request to carry out~~ the details of any** medicinal product-specific validation studies **~~carried out to~~** to replace animal-based control methods with non-animal-based control methods.

5. When adopting its opinion, the Committee for Medicinal Products for Human Use shall include the criteria for the prescription or use of the medicinal products in accordance with Article 50(1) of [revised Directive 2001/83/EC].

CHAPTER XIV
AMENDMENTS TO OTHER LEGAL ACTS

Article 177

Amendments to Regulation (EU) No 536/2014

Regulation (EU) No 536/2014 is amended as follows:

(1) the following Article 5a is inserted:

'*Article 5a*

Environmental risk assessment for investigational medicinal products for human use containing or consisting of genetically modified organisms

1. Where the application according to Article 5 of this Regulation concerns clinical trials with investigational medicinal products for human use containing or consisting of genetically modified organisms (GMOs) within the meaning of Article 2 of Directive 2001/18/EC of the European Parliament and of the Council*, the sponsor shall submit an environmental risk assessment (ERA) in the EU portal (CTIS) **as part of the application**.

2. The ERA referred to in paragraph 1 shall be conducted in accordance with the principles ~~**requirements**~~ set out in Annex II to Directive 2001/18/EC and the scientific guidelines developed by the Agency in coordination with the competent authorities of the Member States, established according to Directive 2001/18/EC for this purpose and the delegated act referred to in paragraph 8.

3. Articles 6 to 11 of Directive 2001/18/EC shall not apply to investigational medicinal products for human use containing or consisting of genetically modified organisms.

4. The Committee for Medicinal Products for Human Use (CHMP) **referred to in Article 148 (revised Regulation No (EC) 726/2004]** shall assess the ERA referred to in paragraph 1 in the form of a scientific opinion. The CHMP shall submit its opinion to the competent authority of the Reporting Member State within ~~45~~ **38** days from the validation date referred to in Article 5(3). Where appropriate, the opinion shall include risk mitigation measures. The sponsor shall provide evidence to the Reporting Member State and the Member States Concerned that these measures will be implemented.

5. The CHMP may request, with justified reasons, via the EU portal (CTIS) additional information from the sponsor regarding the assessment referred to in paragraph 1, which shall be provided only within the period referred to in **Article 6,** paragraph 5.

6. To obtain and review the additional information referred to in paragraph ~~6~~**5**, the Agency may extend the period referred to in paragraph 5 by a maximum of 31 days. The sponsor shall submit the requested additional information within the period set by the Agency. Where the sponsor does not provide additional information within the period set by the Agency, the application referred to in paragraph 1 shall be deemed to have expired in all Member States concerned. **The Agency shall inform the reporting Member State via the CTIS and the Member States concerned about the extension of the period referred to in paragraph 5 in accordance with this paragraph as well as the period set for the sponsor to submit the requested information.**

7. In case of first-in-class products or when a novel question arises during the assessment of the submitted ERA as referred to in paragraph 1, the Agency shall ~~**may**~~**, if ~~as~~ necessary,** consult with bodies that Member States have set up in accordance with Directive 2001/18/EC or Directive 2009/41/EC of the European Parliament and of the Council**. If a consultation is necessary, the technical dossier addressing in sufficient detail the information specified in Annex III to Directive 2001/18/EC should be included to support the ERA where appropriate.

8. The Commission shall be empowered to adopt a delegated act in accordance with Article 89 to amend the Annexes to this Regulation in order to specify the procedure for the submission and the harmonized assessment of the ERA for investigational medicinal products containing or consisting of GMOs as set out in paragraphs 1 to 8.

The delegated act referred to in the first subparagraph shall establish that the ERA is an independent part of the application.

The delegated act referred to in the first subparagraph shall specify the content of the ERA taking into account the common application forms and Good Practice Documents for genetically modified human cells and for adeno-associated viral vectors that were published by the Agency.

The delegated act referred to in the first subparagraph shall contain a provision to update the ERA requirements for investigational medicinal products containing or consisting of GMOs following scientific developments and changes of (Directive 2001/18/EC).';

* 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 - Commission Declaration (OJ L 106, 17.4.2001, p. 1).

** Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (Recast) (OJ L 125, 21.5.2009, p. 75).';

(2) in Article 25(1), point (d), is replaced by the following:

'(d) measures to protect subjects, third persons and the environment;';

(3) Article 26 is replaced by the following:

'*Article 26*

Language requirements

The language of the application dossier, or parts thereof, shall be determined by the Member State concerned.

The language for the environmental risk assessment (ERA) shall preferably be English. Member States, in applying the first subparagraph, shall consider accepting, for the documentation not addressed to the subject, a commonly understood language in the medical field.';

(4) in Article 37(4), the following subparagraph is inserted after the first subparagraph:
In the case of a clinical trial which involves the use of a medicinal product in the paediatric population, the timeline referred to in the first subparagraph to submit to the EU database a summary of the results of the clinical trial shall be 6 months.';

(5) in Article 61(2), point (a), is replaced by the following:

'(a) it shall have at its disposal, for manufacture or import, suitable and sufficient premises, technical equipment and control facilities complying with the requirements set out in this Regulation and, where appropriate, in case of investigational medicinal products containing or consisting of GMOs, in Directive 2009/41/EC;';

(6) in Article 66(1), point (c), is replaced by the following:

(c) information to identify the medicinal product, including, where appropriate, 'This IMP contains genetically modified organisms;';

(7) in Article 76, paragraph (1) is replaced by the following:

'1. Member States shall ensure that systems for compensation for any damage suffered by a subject resulting from the participation in a clinical trial ~~or caused to third persons or the environment during such trial~~ conducted on their territory are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk.';

(8) Article 89 is replaced by the following:

'*Article 89*

Exercise of the delegation

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 Articles 5a, 27, 39, 45, 63(1) and 70 shall be conferred on the Commission for a period of five years from the date referred to in Article 99(2). The Commission shall draw up a report in respect of the delegated powers not later than nine months before the end of the five year period. The delegation of powers 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.

3. The delegation of power referred to in Articles 5a, 27, 39, 45, 63(1), and 70 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 Articles 5a, 27, 39, 45, 63(1), and 70 shall enter into force only if no objection has been expressed either by the European Parliament or 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 the Council.';

(9) Article 91 is replaced by the following:

'*Article 91*

Relation with other Union legal acts

'This Regulation shall be without prejudice to Council Directive 97/43/Euratom[29], Council Directive 96/29/Euratom[30], Directive 2004/23/EC of the European Parliament and of the Council[31], Directive 2002/98/EC of the European Parliament and of the Council[32] and Directive 2010/53/EU of the European Parliament and of the Council[33].

In the context of inspections referred under Articles 52(5) of [revised Regulation 726/2004] and Article 78 of this Regulation and the criteria set out in Annex III of [revised Regulation 726/2004] apply mutatis mutandis.'

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29 Council Directive 97/43/Euratom of 30 June 1997 on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, and repealing Directive 84/466/Euratom (OJ L 180, 9.7.1997, p. 22).

30 Council Directive 96/29/Euratom of 13 May 1996 laying down basic safety standards for the protection of the health of workers and the general public against the dangers arising from ionizing radiation (OJ L 159, 29.6.1996, p. 1).

31 Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (OJ L 102, 7.4.2004, p. 48).

32 Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (OJ L 033, 8.2.2003, p. 30).

33 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).

Chapter II
GENERAL PROVISIONS AND RULES ON APPLICATIONS

Section 2
Marketing authorisation decisions

Article 13

Commission decision on the marketing authorisation

1. Within 12 days of receipt of the opinion of the Committee for Medicinal products for Human Use the Commission shall submit to the Standing Committee on Medicinal Products for Human Use referred to in Article 173(1) a draft of the decision on the application.

   In duly justified cases, the Commission may return the opinion to the Agency 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 12(4).

   Where a draft decision envisages the granting of a marketing authorisation subject to the conditions referred to in Article 12(4), points (c) to (j), it shall lay down deadlines for the fulfilment of the conditions, where necessary.

   Where the draft decision differs from the opinion of the Agency, the Commission shall provide a detailed explanation of the reasons for the differences.

   The Commission shall send the draft decision to the Member States and the applicant.

2. The Commission shall, by means of implementing acts, take 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 173, paragraphs 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 delivered by the Agency, the Commission may refer the application back to the Agency 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.

4. The Agency shall disseminate the documents referred to in Article 12(4), points (a) to (e), together with any deadlines laid down pursuant to paragraph 1, first subparagraph.

Article 14

Withdrawal of a marketing authorisation application

If an applicant withdraws an application for a marketing authorisation submitted to the Agency before an opinion has been given on the application, the applicant shall communicate its reasons for doing so to the Agency. The Agency shall make this information publicly available and shall publish the assessment report, if available, after deletion of all information of a commercially confidential nature.

Article 15

Refusal of a centralised marketing authorisation

1. The marketing authorisation shall be refused if, after verification of the particulars and documentation submitted in accordance with Article 6, the view is taken that:
   (a) the benefit-risk balance of the medicinal product is not favourable;
   (b) that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product;
   (c) its qualitative and quantitative composition is not as declared;
   (d) the environmental risk assessment is incomplete or insufficiently substantiated by the applicant or if the risks identified in the environmental risk assessment have not been sufficiently addressed by the applicant**, unless ~~a~~ post-authorisation environmental risk assessment studies can be requested or the identified risks can be mitigated with appropriate risk mitigation measures**;

(e) particulars or documentation provided by the applicant in accordance with Article 6, paragraphs 1 to 4, are incorrect;

(f) the labelling and package leaflet proposed by the applicant are not in accordance with Chapter VI of [revised Directive 2001/83/EC].

2. The refusal of a Union marketing authorisation shall constitute a prohibition on the placing on the market of the medicinal product concerned throughout the Union.

3. Information about all refusals and the reasons for them shall be made publicly available.

Article 16

Marketing authorisations

1. Without prejudice to Article 1, paragraphs 8 and 9 of [revised Directive 2001/83/EC], a marketing authorisation which has been granted in accordance with this Regulation shall be valid throughout the Union. It shall confer the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State in accordance with Article 5 of [revised Directive 2001/83/EC].

The Commission shall ensure that authorised medicinal products for human use are added to the Union Register of Medicinal Products and that they are given a number, which shall appear on the packaging.

2. Notification of marketing authorisation shall be published in the *Official Journal of the European Union*, quoting the date of marketing authorisation and the registration number in the Union Register of Medicinal Products, any International Non-proprietary Name (INN) of the active substance of the medicinal product, its pharmaceutical form, and any Anatomical Therapeutic Chemical Code (ATC).

3. The Agency shall immediately publish the assessment report on the medicinal product for human use and the reasons for its opinion in favour of granting marketing authorisation, after deletion of any information of a commercially confidential nature. **The justification for a marketing authorisation under exceptional circumstances and the justification for a conditional marketing shall be included in the assessment report.**

   The European public assessment report (EPAR) shall include:
   - a summary of the assessment report 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;
   - a summary of environmental risk assessment studies and their results as submitted by the marketing authorisation holder and the assessment of the environmental risk assessment and the information referred to in Article 22(5) of [revised Directive 2001/83/EC] by the Agency.

4. ***(discussed in the shortage cluster)***

Article 17

Validity and renewal of marketing authorisations

1. Without prejudice to paragraph 2, a marketing authorisation for a medicinal product shall be valid for an unlimited period.

2. By way of derogation from paragraph 1, the Commission may decide when granting an authorisation, on the basis of a scientific opinion by the Agency concerning the safety of the medicinal product, to limit the validity of the marketing authorisation to five years.

   Where the validity of the marketing authorisation is limited to five years, the marketing authorisation holder shall apply to the Agency for a renewal of the marketing authorisation at least nine months before the marketing authorisation ceases to be valid.

Where a renewal application has been submitted in accordance with the second subparagraph, the marketing authorisation shall remain valid until a decision is adopted by the Commission in accordance with Article 13.

The marketing authorisation may be renewed on the basis of a re-evaluation by the Agency of the benefit-risk balance. Once renewed, the marketing authorisation shall be valid for an unlimited period.

Article 18

Marketing authorisation granted in exceptional circumstances

1. In exceptional circumstances where, in an application under Article 6 of [revised Directive 2001/83/EC] for a marketing authorisation of a medicinal product or a new therapeutic indication of an existing marketing authorisation under this Regulation, an applicant is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, the Commission may, by derogation to Article 6, grant an authorisation under Article 13, subject to specific conditions, where the following requirements are met:
   (a) the applicant has demonstrated, in the application file, that there are objective and verifiable reasons not to be able to submit comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use based on one of the grounds set out in Annex II to [revised Directive 2001/83/EC];
   (b) except for the data referred to in point (a), the application file is complete and satisfies all the requirements of this Regulation;
   (c) specific conditions are included in the decision of the Commission, in particular to ensure the safety of the medicinal product as well to ensure that the marketing authorisation holder notifies to the competent authorities any incident relating to its use and takes appropriate action where necessary.

2. The maintenance of the authorised new therapeutic indication and the validity of the marketing authorisation granted in accordance with paragraph 1 shall be linked to the reassessment by the Agency of the conditions referred to in paragraph 1 after two years **or at an earlier time as set out in the marketing authorisation,** from the date when the new therapeutic indication was authorised or the marketing authorisation was granted, and thereafter at a risk-based frequency to be determined by the Agency and specified by the Commission in the marketing authorisation.

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

~~**3. The justification for a marketing authorisation under exceptional circumstances shall be included in the European public assessment report.**~~

Article 19

Conditional marketing authorisation

1. In duly justified cases, to meet an unmet medical need of patients~~, as referred to in Article 83(1), point (a), of [revised Directive 2001/83/EC]~~, a conditional marketing authorisation or a new conditional therapeutic indication to an existing marketing authorisation authorised under this Regulation may be granted by the Commission to a medicinal product that is likely to address the unmet medical need in accordance with Article 83(1)~~, point (b)~~, of [revised Directive 2001/83/EC], prior to the submission of comprehensive clinical data provided that the benefit of the immediate availability on the market of that medicinal product outweighs the risk inherent in the fact that additional data are still required.

In emergency situations, a conditional marketing authorisation or a new conditional therapeutic indication referred to in the first subparagraph may be granted also where comprehensive non-clinical or pharmaceutical data have not been supplied.

2. Conditional marketing authorisations or a new conditional therapeutic indication referred to in paragraph 1 may be granted only if the benefit-risk balance of the medicinal product is favourable and the applicant is likely to be able to provide comprehensive data. ~~**The justification for a conditional marketing authorisation must be included in the European public assessment report.**~~

3. Conditional marketing authorisations or a new conditional therapeutic indication granted pursuant to this Article shall be subject to specific obligations. Those specific obligations and, where appropriate, the time limit for compliance shall be specified in the conditions to the marketing authorisation. Those specific obligations shall be reviewed annually by the Agency ~~for the first three years after granting the authorisation and every two years thereafter~~.

4. As part of the specific obligations referred to in paragraph 3, the marketing authorisation holder of a conditional marketing authorisation granted pursuant to this Article shall be required to complete ongoing studies, or to conduct new studies, with a view to confirming that the benefit-risk balance is favourable.

5. The summary of product characteristics and the package leaflet shall clearly mention that the conditional marketing authorisation for the medicinal product has been granted subject to specific obligations as referred to in paragraph 3.

6. By way of derogation from Article 17(1), an initial conditional marketing authorisation granted pursuant to this Article shall be valid for ~~one~~ two years, ~~on a~~ with the possibility of an extension of up to ~~renewable basis for the first~~ three years~~-~~ not to exceed an overall duration of 5 years after granting the authorisation~~, and every two years thereafter.~~

7. When the specific obligations referred to in paragraph 3 have been fulfilled for a conditional marketing authorisation granted pursuant to this Article, the Commission may, following an application by the marketing authorisation holder, and after having received a favourable opinion from the Agency, grant a marketing authorisation pursuant to Article 13.

Commented [A3]: SI would support the inclusion of a provision where the validity of the CMA should be limited to two years (instead of current one year). SI would furthermore support the renewal for a maximum of 3 years and overall duration of CMA i.e. 5 years. In this period, the CHMP can either confirm the marketing authorisation (converting the CMA into a standard marketing authorisation) or recommend revoking/not confirming it.

Therapeutic continuity must be guaranteed in case the CMA is not converted into standard marketing authorisation and the medicinal product is withdrawn from the market. Therapeutic continuity must be ensured and therefore specifically defined in new compromise text.

8. The Commission is empowered to adopt delegated acts in accordance with Article 175 to supplement this Regulation by establishing the following:
   (a) the categories of medicinal products to which paragraph 1 applies;
   (b) the procedures and requirements for granting a conditional marketing authorisation, for its renewal, and for adding a new conditional therapeutic indication to an existing marketing authorisation.

Article 20

Imposed post-authorisation studies

1. After the granting of a marketing authorisation, the Agency may consider that it is necessary that the marketing authorisation holder:
   (a) conducts 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 Agency shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study;
   (b) conducts 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 21 while taking into account the scientific guidance referred to in Article 123 of [revised Directive 2001/83/EC];
   (c) conducts a post-authorisation environmental risk assessment study to further investigate the risks to the environment or public health due to the release of the medicinal product in the environment, if new concerns emerge on the authorised medicinal product, or other medicinal products containing the same active substance~~;~~.

   If this obligation would apply to several medicinal products, the Agency shall encourage the marketing authorisation holders concerned to conduct a joint post authorisation environmental risk assessment study.

(d) **conducts a post-authorisation study to improve the safe and effective use of the medicinal product.**

Where the Agency considers that any of the post-authorisations studies referred to in points (a) to (**d**~~e~~) is necessary, it shall inform the marketing authorisation holder thereof in writing, stating the grounds for its assessment and shall include the objectives and timeframe for submission and conduct of the study.

2. The Agency shall provide the marketing authorisation holder with an opportunity to present written observations in response to its letter within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the letter.

3. On the basis of the written observations the Agency shall review its opinion.

4. Where the opinion of the Agency confirms the need for any of the post-authorisation studies referred to in paragraph 1, points (a) to (c), to be carried out, the Commission shall vary the marketing authorisation, by means of implementing acts, adopted pursuant to Article 13 to include the obligation as a condition of the marketing authorisation unless the Commission returns the opinion to the Agency for further consideration. For obligations under paragraph 1, points (a) and (b), the marketing authorisation holder shall update the risk management system accordingly.

Article 21

Post authorisation efficacy studies

The Commission is empowered to adopt delegated acts in accordance with Article 175, to supplement this Regulation by determining the situations in which post-authorisation efficacy studies may be required under Article 12(4), point (g), and Article 20(1), point (b).

Article 22

Risk management system

The marketing authorisation holder shall incorporate any condition of authorisation reflecting the elements referred to in Article 12(4), points (d) to (g), or in Article 20, or in Article 18(1) and Article 19 in their risk management system.

Article 23

Liability of the marketing authorisation holder

The granting of a marketing authorisation shall not affect the civil or criminal liability of the manufacturer or of the marketing authorisation holder pursuant to the applicable national law in Member States.

Article 25

Duplicate marketing authorisations

1. Only one marketing authorisation may be granted to an applicant for a specific medicinal product.

   By way of derogation from the first subparagraph, the Commission shall authorise the same applicant to submit more than one application to the Agency for that medicinal product in either of the following cases:

   (a) if one of its indications or pharmaceutical forms~~, methods or routes of administration or any other way in which the medicinal product may be used~~ is protected by a patent or a supplementary protection certificate in one or more Member States. Parts of the text necessary for the safe use of the medicinal product shall not be omitted in the product information of the duplicate marketing authorisation;

   (b) for reasons of co-marketing with a different undertaking not belonging to the same group as the marketing authorisation holder of the medicinal product for which a duplicate is requested.

Commented [A4]: SI: In our opinion, it is not acceptable that the scope has been extended to "posologies, methods or routes of administration or any other way in which the medicinal product may be used".

Parts of the text necessary for the safe use of the medicinal product shall not be omitted in the product information of the duplicate MA.

As soon as the relevant patent or supplementary protection certificate referred to in point (a) expires, the marketing authorisation holder shall withdraw or vary the initial or duplicate marketing authorisation.

Commented [A5]: SI: The proposal for a new regulation requires the MAH to cancel duplicate CP marketing authorisation (without the possibility of variation) as soon as patent protection expires. In practice, this would mean that the supply of a medicine for several markets would be instantly interrupted, as all lists, prices, tenders and contracts,... are linked to the MA number, which the MAH will be forced to cancel.

It is desirable to maintain the status quo; i.e. that MAH files the appropriate variations when the patent protection expires but is not forced to withdraw the marketing authorisation.

2. As regards medicinal products for human use, Article 187(3) of [revised Directive 2001/83/EC] shall apply to medicinal products authorised under this Regulation.

3. Without prejudice to the unique Union nature of the content of the documents referred to in Article 12(4), points (a) to (k), this Regulation shall not prohibit the use of two or more commercial designs for a given medicinal product for human use covered by a single marketing authorisation.

Article 26

Medicinal products for compassionate use

1. ~~By way of derogation from Article 5 of [revised Directive 2001/83/EC]~~ Member States may make available for compassionate use a medicinal product for human use belonging to the categories referred to in Article 3, paragraphs 1 and 2. This may include new therapeutic uses of an authorised medicinal product.

2. For the purposes of this Article, 'compassionate use' shall mean making a medicinal product belonging to the categories referred to in Article 3, paragraphs 1 and 2 available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorisation in accordance with Article 6 or the submission of such application is imminent, or it must be undergoing clinical trials in the same indication.

3. When applying paragraph 1, the Member State shall notify the Agency.

4. When compassionate use is envisaged by a Member State, the Committee for Medicinal Products for Human Use, after consulting the manufacturer or the applicant, may adopt opinions on the conditions for use, the conditions for distribution ~~and~~**,** the patients targeted **and the conditions of monitoring**. The opinions shall be updated where necessary.

In the preparation of the opinion, the Committee for Medicinal Products for Human Use may request information and data from marketing authorisation holders and from developers and may engage with them in preliminary discussions. The Committee may also make use of health data generated outside of clinical studies, where available, taking into account the reliability of those data.

The Agency may also liaise with the third country agencies for medicinal products with respect to additional information and data exchanges.

In the preparation of its opinion, the Committee for Medicinal Products for Human Use may consult the Member State concerned and request it to provide any available information or data that the Member State has in its possession relating to the medicinal product concerned.

5. **When applying paragraph 1,** Member States shall take account of any available opinion and notify the Agency of the making available of products on the basis of the opinion in their territory. Member States shall ensure that pharmacovigilance requirements ~~are applied for those products. Article 106, paragraphs 1 and 2,~~ as regards the recording and reporting of suspected adverse reactions and the submission of ~~periodic~~ safety ~~update~~ reports **are applied for those products**~~respectively, shall apply *mutatis mutandis*~~.

6. The Agency shall keep an up-to-date list of the opinions adopted in accordance with paragraph 4 and shall publish it on its website.

7. The opinions referred to in paragraph 4 shall not affect the civil or criminal liability of the manufacturer or of the applicant for marketing authorisation.

8. Where a compassionate use programme has been set up in accordance with paragraphs 1 and 5, the applicant shall ensure that patients taking part also have access to the new medicinal product **if necessary until the medicine is made available on the market of the Member State concerned.** ~~**until the end of the in the course of their treatment, including the case when the compassionate use progamme has ended.** during the period between authorisation and placing on the market.~~

9. This Article shall be without prejudice to Regulation (EU) No 536/2014 and to Article 3 of [revised Directive 2001/83/EC].

10. The Agency may adopt detailed guidelines laying down format and content of notifications referred to in paragraphs 3 and 5, and data exchange under this Article.

Article 27

Request for opinion on scientific matters

At the request of the Executive Director of the Agency or the Commission, the Committee for Medicinal Products for Human Use shall draw up an opinion on any scientific matter concerning the evaluation of medicinal products for human use. That Committee shall take due account of any requests by Member States for an opinion.

The Agency shall publish the opinion after deletion of any information of a commercially confidential nature.

Article 28

Regulatory decisions on marketing authorisations

An authorisation to place a medicinal product covered by this Regulation on the market shall not be granted, refused, varied, suspended, withdrawn or revoked except through the procedures and on the grounds set out in this Regulation.

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Chapter I:
Subject matter, scope and definitions

Article 4

Definitions

(12) 'reference medicinal product' means a medicinal product that is or has been ~~**granted a marketing authorisation by a Member State or by the Commission on the basis of a complete dossier, including the submisson of quality, pre-clinical and clinical data**~~ authorised **by a Member State or by the Commission** ~~in the Union~~ under Article 5, in accordance with Article 6~~**, 13 or 14**~~;

(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) 'letter of access' means an original document, signed by the owner of the data or its representative, that states that the data may be used for the benefit of a third party by a competent authority or the Commission for the purposes of this Directive;

(16) '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;

Commented [A6]: RED LINE:
SI is reserved on the proposed revised definition. Legal basis of well-established-use (Art 13) and informed consent (Art 14) should be covered by this definition. Which is not the case with the proposed amendment.

Rationale:
In the past many reference medicinal products were authorised in accordance with "well-established-use" legal basis. Availability of generics would be jeopardized in small MS. This is also in line with CJEU judgement Olainfarm C-104/13

(17) ‘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 for medical purposes simultaneously or sequentially administered;

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

(19) ‘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;

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

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

(22) ‘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 ~~and,~~ antifungals **and antiprotozoals**;

(23) ‘integral combination of a medicinal product with a medical device’ means a combination of a medicinal product with a medical device, as defined by Regulation (EU) 2017/745, and where:

(a) the two form an integral product and where 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.

(25) ‘medicinal product in exclusive use with a medical device’ means a medicinal product presented in a package with a medical device or to be used with a specific medical device, as defined by Regulation (EU) 2017/745, ~~of~~ **or with an in-vitro diagnostic medical device as defined by Regulation (EU) 2017/746,** and referenced in the summary of product characteristics;

(26) ‘combination of a medicinal product with a product other than a medical device’ means a combination of a medicinal product with a product other than a medical device (as defined by Regulation (EU) 2017/745) and where the two are intended for use in the given combination in accordance with the summary of product characteristics;

(33) ‘environmental risk assessment’ means the evaluation of the risks to the environment, or risks to public health, posed by the release of the medicinal product in the environment ~~from~~ **following** the use and disposal of the medicinal product and the identification of risk prevention, limitation and mitigation measures. For ~~medicinal product with an~~ antimicrobial**s** ~~mode of action~~, the ERA also encompasses an evaluation of the risk for antimicrobial resistance selection in the environment due to the manufacturing, use and disposal of that medicinal product;

(34) ‘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 sufficient to inhibit or kill that micro-organism;

(35) ‘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 in the environment including anti-microbial resistance;

(36) 'active substance master file' means a document that contains a detailed description of the manufacturing process, quality control during manufacture and process validation prepared in a separate document by the manufacturer of the active substance;

(41) 'benefit-risk balance' means an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks referred to in point (35), subpoint (a);

(XX) 'biosimilar medicinal product' means a biological medicinal product that is similar to a reference medicinal product and has the same strength, pharmaceutical form, route of administration ~~and therapeutic indications~~;

POST-MARKETING AUTHORISATIONS, RESTRICTIONS AND VARIATIONS

RECITALS

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(21) Marketing authorisation decisions should be taken on the basis of the objective scientific criteria of 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 medicinal products.

(22) The particulars and documentations that are to accompany an application for marketing authorisation for a medicinal product demonstrate that the therapeutic efficacy of the product overweight potential risks. The benefit-risk balance of all medicinal products will be assessed when they are placed on the market, and at any other time the competent authority deems appropriate.

(34) 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. The legislation should allow under similar circumstances for medicinal products with a standard marketing authorisation for new therapeutic indications to be authorised on a conditional basis or under exceptional circumstances. The 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 shall be subject to specific review of the fulfilment of the imposed specific conditions or obligations. The grounds for refusal of a marketing authorisation should apply mutatis mutandis for such cases.

(80) In the event of a risk to public health, the marketing authorisation holder or the competent authorities should be able to make urgent safety or efficacy restrictions on their own initiative. In such case, when the referral procedure is launched, any duplication of assessment should be avoided.

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

(95) The terms of a marketing authorisation for a medicinal product may 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 these 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 competent authorities.

(96) Scientific and technological progresses in data analytics and data infrastructure provide valuable support to the development, 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 this basis, competent authorities of the Member States should take initiative to update the summary of product characteristics in case new efficacy or safety data impacts the benefit-risk balance of a medicinal product.

(142) 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 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. In order to ensure that the data supporting the marketing authorisation concerning the use of a product in children **are adequate**, the competent authorities responsible for the authorisation of a medicinal product should check compliance with the agreed paediatric investigation plan and any waivers and deferrals at the validation step for marketing authorisation applications.

(144) 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 variation of existing marketing authorisations.

(146) Due to the need to reduce overall approval times for medicinal products, the time between the opinion of the Committee for Medicinal Products for Human Use (CHMP) and the final decision on any Commission Decision concerning national marketing authoristions, in particular for referrals, should be reduced to, in principle, 46 days.

(147) On the basis of the opinion of the Agency, the Commission should adopt a decision on the referral by means of implementing acts. In justified cases, the Commission may return the opinion for further examination or deviate in its decision from the opinion of the Agency. Taking into account the need to make medicinal products swiftly available to patients, it should be acknowledged that the chairperson of the Standing Committee for Medicines for Human Use will use the available mechanisms under Regulation 182/2011 and notably the possibility to obtain the committees opinion in written procedure and within expeditious deadlines which, in principle, will not exceed 10 calendar days.

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(85) Where the Commission considers that there are reasons to believe that a medicinal product could present a potential serious risk to human health, a scientific evaluation of the medicinal product should be undertaken by the Agency, leading to a decision whether to maintain, vary, suspend or revoke the marketing authorisation, and taken on the basis of an overall benefit-risk assessment. The Commission may also act on a centralised marketing authorisation where the conditions attached to it are not complied with.

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Chapter VIII
Post-marketing authorisation measures

Article 87

Imposed post-authorisation studies

1. After the granting of a 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 88 while taking into account the scientific guidance referred to in Article 123;
   (bad) 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;
   (c) to conduct a post-authorisation environmental risk assessment study, collection of 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** ~~related~~ active substance;

If the same concerns apply to more than one medicinal product, **and post-authorisation studies are considered necessary,** the competent authority of Member State shall, following consultation with the Agency, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation ~~environmental risk assessment~~ study.

The imposition of such an obligation 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 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.

3. On the basis of the written observations submitted by the marketing authorisation holder, the competent authority of the Member State shall withdraw or confirm the obligation. Where the competent authority of the Member State confirms the obligation, the marketing authorisation shall be varied to include the obligation as a condition of the marketing authorisation and, where appropriate, the risk management system shall be updated accordingly.

Article 88

Delegated acts on post-authorisation efficacy studies

1. In order to determine the situations in which post-authorisation efficacy studies may be required under Articles 44 and 87, the Commission may adopt, by means of delegated acts in accordance with Article 215, measures supplementing the provisions in Articles 44 and 87.

2. When adopting such delegated acts, the Commission shall act in accordance with the provisions of this Directive.

Article 89

Recording of conditions related to marketing authorisations

1. The marketing authorisation holder shall incorporate any safety or efficacy conditions referred to in Articles 44, 45 and 87 **paragraph 1, points (a), ~~and~~ (b) and (ba)** in the risk management system.

2. ~~The Member States shall inform the Agency of the marketing authorisations that they have granted subject to conditions pursuant to Articles 44, 45 and of any obligations imposed in accordance with Article 87.~~

Article 90

*Update of marketing authorisation related to scientific and technological ~~progress~~ **developments***

1. After a 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 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 concerned.

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 documentations referred to in Articles 6, 9 to 13, 62, 41(5), 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 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 marketing authorisation including the summary of product characteristics, the labelling and 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 104 of [revised Regulation (EC) No 726/2004].

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 a competent authority 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 a competent authority regarding the implementation of any measures previously imposed with regard to risks to the environment or public health, including antimicrobial resistance.

Article 91

Update of risk management plans

1. The marketing authorisation holder of a medicinal product referred to in Articles 9 and 11**,** **who did not submit a risk management plan in accordance with Article 21** 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 9 and 11 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 a marketing authorisation holder for a medicinal product referred to Articles 9 and 11 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 case referred to in paragraph**s 1 and** 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 ~~3~~ **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 by means of a variation.

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CHAPTER IV
POST-MARKETING AUTHORISATION MEASURES

Article 44

Urgent safety or efficacy restrictions

1. If, in the event of a risk to public health, the marketing authorisation holder takes urgent safety or efficacy restrictions on their own initiative, the marketing authorisation holder shall immediately ~~**without undue delay**~~ inform the Agency **and the competent authorities of the Member States where the medicinal product is placed on the market**.

   If the Agency has not raised objections within 24 hours following receipt of the information, the urgent safety or efficacy restrictions shall be deemed temporarily accepted.

   The marketing authorisation holder shall submit the corresponding application for variation within ~~15~~ **12** days following initiation of that restriction in accordance with Article 47.

2. In the event of a risk to public health, the Commission may vary the marketing authorisation to impose urgent safety or efficacy restrictions on the marketing authorisation holder.

   The Commission shall take the decision to amend the marketing authorisation by means of implementing acts.

   Where the Commission decision in accordance with this Article imposes restrictions with regard to the safe and effective use of the medicinal product, it may also adopt a decision addressed to the Member States pursuant to Article 57.

Where the marketing authorisation holder disagrees with the Commission decision, they may provide to the Agency written observations on the variation within ~~15~~ **12** days of their receipt of the Commission decision. The Agency shall, based on the written observation, issue an opinion whether an amendment of the variation is required.

If an amendment of the variation is required, the Commission shall take a final decision in accordance with the examination procedure referred to in Article 173(2).

If a referral under Article 55 of this Regulation or under Article 95 or 114 of [revised Directive 2001/83/EC] is launched on the same safety or efficacy concern covered by this variation, any written observation provided by the marketing authorisation holder shall be considered in that referral.

Article 45

Update of a marketing authorisation related to scientific and technological developments

1. After a marketing authorisation has been granted in accordance with this Regulation, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in Annex I, points (6) and (10), to [revised Directive 2001/83/EC], take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. The marketing authorisation holder shall apply for approval of corresponding variations in accordance with Article 47 of this Regulation.

2. The marketing authorisation holder shall without undue delay provide the Agency, the Commission and the Member States with any new information which might entail the amendment of the particulars or documentation referred to in Annex I, Articles 11, 28, 41 **(5)** or 62 of [revised Directive 2001/83/EC], in Annex II to that Directive, or in Article 12(4) of this Regulation.

The marketing authorisation holder shall without undue delay inform the Agency ~~and~~, the Commission **and the competent authorities of the Member States** 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 which 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 indications and populations, whether or not included in the 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 ~~product information and the~~ terms of the marketing authorisation including the summary of product characteristics, the labelling and package leaflet are kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal set-up in accordance with Article 104.

4. The Agency 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 promptly any such request. The marketing authorisation holder shall also respond fully and within the time limit set to any request of a competent authority regarding the implementation of any measures previously imposed, including risk minimisation measures.

   The Agency 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.

   The marketing authorisation holder shall also respond fully and within the time limit set to any request of a competent authority regarding the implementation of any measures previously imposed with regard to risks to the environment or public health, including antimicrobial resistance.

4a. The Agency, through its scientific committees, may consider additional evidence available, independently from the data submitted by the marketing authorisation applicant or marketing authorisation holder. On that basis, if the additional evidence has an impact on the benefit-risk balance of a medicinal product, the Agency may recommend that the summary of product characteristics shall be updated. In this case the marketing authorisation holder shall submit to the Agency an appropriate application for a variation, including an updated summary of product characteristics."

Article 46

Update of risk management plans

1. The marketing authorisation holder of a medicinal product referred to in Articles 9~~,~~ and 11 of [revised Directive 2001/83/EC]**, ~~which~~ who did not submit a risk management plan in accordance with 21 of [Revised Directive 2001/83/EC]** shall submit to the Agency 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 9 and 11 of [revised Directive 2001/83/EC] is maintained.

   The risk management plan and the summary thereof shall be submitted to the Agency within 60 days of the withdrawal of the marketing authorisation for the reference medicinal product by means of a variation in accordance with Article 47.

2. The Agency may impose an obligation on a marketing authorisation holder for a medicinal product referred to in Articles 9~~, 10,~~ **and** 11 ~~and 12~~ of [revised Directive 2001/83/EC] 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 case mentioned referred to in paragraph**s 1 and** 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 ~~3~~**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 by means of a variation in accordance with Article 47.

Article 47

Variation of marketing authorisation

1. An application for variation of a centralised 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 the terms of the 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 Agency. 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 175 to supplement this Regulation by establishing the following:
   (a) the categories referred to in paragraph 2 in which variations shall be classified;
   (b) procedures for the examination of applications for variations to the terms of 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 marketing authorisation and for the same change to the terms of several marketing authorisations;

(d) specifying exemptions to the variation procedures where the update of information in the marketing authorisation referred to in Annex ~~I~~**II of the [revised Directive 2001/83]** 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 to the terms of marketing authorisation.

Article 49

Transfer of marketing authorisation

1. A marketing authorisation may be transferred to a new marketing authorisation holder. Such a transfer shall not be considered to be a variation. The transfer shall be subject to prior approval by the Commission, by means of implementing acts, following the submission of an application for the transfer to the Agency.

2. The Commission is empowered to adopt delegated acts in accordance with Article 175 to supplement this Regulation by establishing procedures for the examination of applications to the Agency for the transfer of marketing authorisations.

Article 50

Supervisory authority

1. In the case of medicinal products manufactured within the Union, the supervisory authorities for manufacturing shall be the competent authorities of the Member State or Member States which granted the manufacturing authorisation referred to in Article 142(1) of [revised Directive 2001/83/EC] in respect of the medicinal product concerned.

2. In the case of medicinal products imported from third countries, the supervisory authorities for imports shall be the competent authorities of the Member State or Member States that granted ~~the authorisation referred to in Article 142(4~~**3**~~) of [revised Directive 2001/83/EC] to the importer~~ ~~**or the holder of**~~ **the manufacturing authorisation**~~, unless appropriate agreements have been made between the Union and the exporting country to ensure that those controls are carried out in the exporting country and that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Union~~ **to the holder that performs the certification**.

A Member State may request assistance from another Member State or from the Agency.

3. The supervisory authority for pharmacovigilance shall be the competent authority of the Member State in which the pharmacovigilance system master file is located.

Article 51

Responsibilities of the supervisory authorities

1. The supervisory authorities for manufacturing and imports shall be responsible for verifying on behalf of the Union that the marketing authorisation holder for the medicinal product or the manufacturer or importer established within the Union satisfies the requirements concerning manufacturing and imports laid down in Chapters XI and XV of [revised Directive 2001/83/EC].

When carrying out the verification referred to in the first subparagraph, the supervisory authorities may request to be accompanied by a rapporteur or expert appointed by the Committee for Medicinal Products for Human Use or by an inspector of the Agency.

The supervisory authorities for pharmacovigilance shall be responsible for verifying on behalf of the Union that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements laid down in Chapters IX and XV of [revised Directive 2001/83/EC].

The supervisory authorities for pharmacovigilance may, if necessary, conduct pre-authorisation inspections to verify the accuracy and successful implementation of the pharmacovigilance system as it has been described by the applicant in support of their application.

2. Where, in accordance with Article 202 of [revised Directive 2001/83/EC], the Commission is informed of serious differences of opinion between Member States as to whether the marketing authorisation holder for the medicinal product for human use or a manufacturer or importer established within the Union satisfies the requirements referred to in paragraph 1, the Commission may, after consultation with the Member States concerned, request an inspector from the supervisory authority to undertake a new inspection of the marketing authorisation holder, the manufacturer or the importer.

   The inspector in question ~~shall~~ **may** be accompanied by two inspectors from Member States which are not party to the dispute or by two experts nominated by the Committee for Medicinal Products for Human Use.

3. ~~Taking into account~~ **Without prejudice to** any agreements which may have been concluded between the Union and third countries in accordance with Article 50, the Commission may, following a reasoned request from a Member State or from the Committee for Medicinal Products for Human Use, or on its own initiative, require a manufacturer established in a third country to submit to an inspection.

   The inspection shall be requested to the supervisory authority referred to in Article 50 (2). The inspection shall be undertaken by inspectors from the Member States who possess the appropriate qualifications. They may request to be accompanied by a rapporteur or expert appointed by the Committee for Medicinal Products for Human Use or by an inspector of the Agency. The report of the inspectors shall be made available electronically to the Commission, the Member States and the Agency.

Article 55

Referral procedure

1. Where the supervisory authorities or the competent authorities of any other Member State are of the opinion that the manufacturer or importer established within the Union territory is no longer fulfilling the obligations laid down in Chapter XI of [revised Directive 2001/83/EC], they shall without undue delay inform the Agency and the Commission, stating their reasons in detail and indicating the course of action proposed.

   Similarly, where a Member State or the Commission considers that one of the measures envisaged in Chapters IX, XIV and XV of [revised Directive 2001/83/EC] is to be applied in respect of the medicinal product concerned or where the Committee for Medicinal Products for Human Use has delivered an opinion to that effect, they shall without undue delay inform each other, as well as the Committee for Medicinal Products of Human Use, stating their reasons in detail and indicating the course of action proposed.

2. In each of the situations described in paragraph 1, the Commission shall request the opinion of the Agency within a time-limit which it shall determine having regard to the urgency of the matter, in order to examine the reasons advanced. Whenever practicable, the marketing authorisation holder for placing the medicinal product for human use on the market shall be invited to provide oral or written explanations.

3. At any stage of the procedure laid down in this Article, following appropriate consultation of the Agency, the Commission may take temporary measures, by means of implementing acts. Those temporary measures shall be applied immediately.

   Without undue delay, the Commission shall, by means of implementing acts, adopt a final decision concerning the measures to be taken in respect of the medicinal product concerned. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

   The Commission may also, pursuant to Article 57, adopt a decision addressed to the Member States.

4. Where urgent action is essential to protect public health or the environment, a Member State may, on its own initiative or at the Commission's request, suspend the use in its territory of a medicinal product for human use which has been authorised in accordance with this Regulation.

   When it does so on its own initiative, it shall inform the Commission and the Agency of the reasons for its action at the latest on the next working day following the suspension. The Agency shall inform the other Member States without delay. The Commission shall immediately initiate the procedure provided for in paragraphs 2 and 3.

5. In cases referred to in paragraph 4, the Member State shall ensure that healthcare professionals are rapidly informed of its action and the reasons for the action. Networks set up by professional associations may be used to this effect. The Member States shall inform the Commission and the Agency of actions taken for this purpose.

6. The suspensive measures referred to in paragraph 4 may be maintained in force until such time as a final decision has been adopted by the Commission in accordance with paragraph 3.

7. The Agency shall, upon request, inform any person concerned of the final decision and make the decision publicly available immediately after it has been taken.

8. Where the procedure is initiated as a result of the evaluation of data relating to pharmacovigilance, the opinion of the Agency, in accordance with paragraph 2, shall be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation from the Pharmacovigilance Risk Assessment Committee and Article 115(2) of [revised Directive 2001/83/EC] shall apply.

9. By way of derogation from paragraphs 1 to 7, where a procedure under Article 95 or Articles 114, 115 and 116 of [revised Directive 2001/83/EC] concerns a range of medicinal products or a therapeutic class, medicinal products that are authorised in accordance with this Regulation and that belong to that range or class shall only be included in the procedure under Article 95, or Articles 114, 115 and 116 of that Directive.

Article 56

Action on conditional marketing authorisation

Where the Agency concludes that a holder of a marketing authorisation granted in accordance with Article 19, including a new therapeutic indication granted referred to Article 19, failed to comply with the obligations laid down in the marketing authorisation, the Agency shall inform the Commission accordingly.

The Commission shall adopt a decision to vary, suspend or revoke that marketing authorisation in accordance with the procedure set out in Article 13.

Article 57

Member State implementation of conditions or restrictions on a Union marketing authorisation

When the Committee for Medicinal Products for Human Use in its opinion refers to recommended conditions or restrictions as provided for in Article 12(4), points (d) to (g), the Commission may adopt a decision addressed to the Member States, in accordance with Article 13 for the implementation of those conditions or restrictions.

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Chapter XV
Restrictions of marketing and manufacturing authorisations

Article 195

Suspending, revoking or varying the terms 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 or that it lacks therapeutic efficacy, or 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 supporting the application as provided for in Articles 6, 9 to 14 or Annexes I to V are incorrect or have not been amended in accordance with Article 90, or where any conditions referred to in Articles 44, 45 and 87 have not been fulfilled or where the controls referred to in Article 191 have not been carried out.

4. Paragraph ~~2~~ **3** also applies 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 described pursuant to Annex I.

5. The competent authorities of the Member State or, in the case of centralised marketing authorisation, the Commission ~~shall~~ **may** suspend or revoke the marketing authorisation for a category of preparations or all preparations where any one of the requirements laid down in Article 143 is no longer met.

Article 196

Prohibition of supply or withdrawal of a medicinal product from the market

1. Without prejudice to the measures provided for in Article 195, 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) it lacks therapeutic efficacy;
   (c) the benefit-risk balance is not favourable;
   (d) its qualitative and quantitative composition is not as declared;
   (e) the controls on the medicinal product or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled; or
   (f) a serious risk to the environment or to public health via the environment has been identified and not sufficiently addressed by the marketing authorisation holder.

2. The competent authority of the Member State 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 authority of the Member State 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 199

Refusal, suspension or revocation within the limits of the Directive

1. A **marketing** authorisation ~~to market~~ **of** 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 importation of medicinal products coming 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 Articles 195(5) and 196.

Chapter VIII

Post-marketing authorisation measures

Article 92

Variation of marketing authorisation

1. An application for variation of a 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 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. 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 215 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 to the terms of 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 marketing authorisation and for the same change to the terms of several marketing authorisations;
   (d) specifying exemptions to the variation procedures where the update of information in the marketing authorisation referred to in Annex II 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 to the terms of marketing authorisation.

Article 93

Variation of marketing authorisation 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 provisions of 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 34 or 36**. The same shall apply where the initial marketing authorisations were granted through separate procedures.

2. In case of arbitration submitted to the Commission, the procedure laid down in Articles 41 and 42 shall apply by analogy to variations made to marketing authorisations.

Article 93a

Variation based on additional evidence

The competent authority of the Member State may consider and 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 authorities may recommend that the summary of product characteristics is updated. In this case the marketing authorisation holder shall submit to the competent authority an appropriate application for a variation, including an updated summary of product characteristics. For medicinal products authorised in accordance with Articles 34 or 36, the reference Member State and all concerned member States shall be involved.

Article 94

Variation of marketing authorisations on the basis of paediatric studies

1. On the basis of relevant paediatric ~~clinical~~ studies received in accordance with Article 45(1) of Regulation (EC) No 1901/2006 of the European Parliament and of the Council[34], 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. The competent authorities shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisations concerned.

2. The activities pursuant to paragraph 1 shall be concluded within five years from [OP please insert the date = 18 months after the date of entering into force of this Directive].

3. When a medicinal product has been authorised under the provisions of Chapter III, on the basis of the information received in accordance with Article 91 of [revised Regulation (EC) No 726/2004], the competent authorities of the Member States may vary the marketing authorisation of the medicinal product concerned accordingly and update the summary of product characteristics and package leaflet.

4. The Member States shall exchange information regarding the **paediatric ~~clinical~~** studies submitted and, as appropriate, their implications for any marketing authorisations concerned.

5. The Agency shall coordinate the exchange of information.

[34] 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).

Article 95

Union interest referral procedure

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 for the application of the procedure laid down in Articles 41 and 42 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 other variation of the marketing authorisation that appears necessary. The Member States and the Commission shall ~~take due account of~~ **consider** any requests by the applicant or the marketing authorisation holder **to initiate 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 115(2) may be applied. The Pharmacovigilance Risk Assessment Committee shall issue a recommendation according to the procedure laid down in Article 41. 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 115 shall apply.

   However, where one of the criteria listed in Article 114(1) is met, the procedure laid down in Articles 114, 115 and 116 shall apply.

   The Member State concerned or the Commission shall clearly identify the question that is referred to the 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 with all available information relating to the matter in question.

2. Where the referral to the Committee concerns a range of medicinal products or a therapeutic class, the Agency may limit the procedure to certain specific parts of the authorisation.

   In that event, Article 93 shall apply to those medicinal products only if they were covered by the 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 covered by a centralised marketing authorisation that belong to that range or 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 **or take other risk minimisation measures** 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 authorisations 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 I:

Subject matter, scope and definitions

Article 4

Definitions

(32) 'risk management plan' means a detailed description of the risk management system;

(54) 'variation' or 'variation of the terms of a marketing authorisation' means any amendment to:

(a) the contents of the particulars and documents referred to in Article 6(2), Articles 9 to 14 and Article 62, Annex I and Annex II thereto and Article 6 of the [revised Regulation (EC) No 726/2004]; or

(b) 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;

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(75) In a situation of public health emergency, it is of major interest for the Union that safe and efficacious medicinal products can be developed and made available within the Union as soon as possible. Agile, fast and streamlined processes are of the essence. A range of measures already exists at Union level to facilitate, support and speed up the development of and granting marketing authorisations for treatments and vaccines during a public health emergency.

(76) It is considered appropriate to also have the possibility for the Commission to grant temporary emergency marketing authorisations to address public health emergencies. Temporary emergency marketing authorisations may be granted provided that, having regard to the circumstances of the public health emergency, the benefit of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent to the fact that additional comprehensive quality, non-clinical, clinical data may still be required. A temporary emergency marketing authorisation should be valid only during the public health emergency. The Commission should be given the possibility to vary, suspend or revoke such marketing authorisations in order to protect public health or when the marketing authorisation holder has not complied with the conditions and obligations set out in the temporary emergency marketing authorisation.

CHAPTER I

SUBJECT MATTER, SCOPE AND DEFINITIONS

Section 3

Temporary emergency marketing authorisation

Article 30

Temporary emergency marketing authorisation

During a public health emergency, the Commission may grant a temporary emergency marketing authorisation ('TEMA') for medicinal products intended for the treatment, prevention or medical diagnosis of a serious or life-threatening disease or condition which are directly related to the public health emergency, prior to the submission of the complete quality, non-clinical, clinical data and environmental data and information.

Where medicinal products containing or consisting of genetically modified organisms in the sense of Article 2(2) of Directive 2001/18/EC are concerned, Articles 13 to 24 of that Directive shall not apply.

An application for a temporary emergency marketing authorisation shall be submitted in accordance with Articles 5 and 6.

Article 31

Criteria for granting a temporary emergency marketing authorisation

A temporary emergency marketing authorisation may be granted only after the recognition of a public health emergency at Union level in accordance with Article 23 of Regulation (EU) 2022/2371 of the European Parliament and of the Council[35] and where the following requirements are met:

(a) there is no other satisfactory method of treatment, prevention or diagnosis authorised or sufficiently available in the Union or, if such method is already available, the temporary emergency marketing authorisation of the medicinal product will contribute to address the public health emergency;

(b) based on the scientific evidence available, the Agency issues an opinion concluding that the medicinal product could be effective in treating, preventing or diagnosing the disease or condition directly related to the public health emergency, and the known and potential benefits of the product outweigh the known and potential risks of the product, taking into consideration the threat posed by the public health emergency.

Article 32

Scientific opinion

1. The Agency shall ensure that the scientific opinion of the Committee for Medicinal Products for Human Use is given without undue delay, taking into account, the recommendation of the Emergency Task Force referred to in Article 38(1), second subparagraph. For the purpose of issuing its opinion, the Agency may consider any relevant data on the medicinal product concerned.

2. The Agency shall review any new evidence provided by the developer, the Member States or the Commission, or any other evidence that comes to its attention, in particular evidence that might influence the benefit-risk balance of the medicinal product concerned.

[35] 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).

The Agency shall update its scientific opinion as necessary.

3. The Agency shall transmit without undue delay to the Commission the scientific opinion and its updates and any recommendations on the temporary emergency marketing authorisation.

Article 33

Commission decision for a temporary emergency marketing authorisation

1. On the basis of the scientific opinion of the Agency or its updates referred to in Article 32, paragraphs 1 and 2, the Commission shall, by means of implementing acts, take a decision without undue delay on the temporary emergency marketing authorisation of the medicinal product subject to the specific conditions set in accordance with paragraphs 2, 3 and 4. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

2. On the basis of the scientific opinion of the Agency referred to in paragraph 1, the Commission shall set specific conditions with respect to the temporary emergency marketing authorisation, in particular the conditions for manufacturing, use, supply and safety monitoring and the compliance with related good manufacturing, and pharmacovigilance practices. If necessary, the conditions may specify the batches of the medicinal product concerned by the temporary emergency marketing authorisation.

3. Specific conditions may be set to require the completion of ongoing studies or to conduct new studies to ensure the safe and effective use of the medicinal product or minimise its impact on the environment. A time limit for the submission of those studies shall be set.

4. Those specific conditions and, where appropriate, the time limit for compliance shall be specified in the conditions to the marketing authorisation and shall be reviewed annually by the Agency.

Article 34

Validity of a temporary emergency marketing authorisation

The temporary emergency marketing authorisation shall cease to be valid when the Commission terminates the recognition of a public health emergency in accordance with Article 23(2) and (4) of Regulation (EU) 2022/2371.

Article 35

Variation, suspension or revocation of a temporary emergency marketing authorisation

The Commission may suspend, revoke or vary the temporary emergency marketing authorisation by means of implementing acts at any time in any of the following cases:

(a) the criteria laid down in Article 31 are no longer met;

(b) it is appropriate to protect public health;

(c) the marketing authorisation holder of a temporary emergency marketing authorisation has not complied with conditions and obligations set out in the temporary emergency marketing authorisation;

(d) the marketing authorisation holder of a temporary emergency marketing authorisation has not complied with the specific conditions set in accordance with Article 33.

Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

Article 36

Granting of a marketing authorisation or conditional marketing authorisation after a temporary emergency marketing authorisation

As soon as sufficient data has been generated, ~~T~~**t**he marketing authorisation holder of an authorisation in accordance with Article 33 ~~may~~ **shall** submit an application in accordance with Articles 5 and 6 in order to **replace the temporary emergency marketing authorisation by** ~~obtain~~ an authorisation in accordance with Articles 13, 16 or 19.

For the purpose of regulatory data protection, the temporary emergency marketing authorisation and any subsequent marketing authorisation, as referred to in subparagraph 1, shall be considered as part of the same global marketing authorisation.

Article 37

Transitional period

When the temporary marketing authorisation of a medicinal product is suspended or revoked for reasons other than the safety of the medicinal product, or if that temporary emergency marketing authorisation ceases to be valid, Member States may, in exceptional circumstances, allow for a transitional period, the supply of the medicinal product to patients who are already being treated with it.

Article 38

Relation with Article 18 of Regulation (EU) 2022/123

1. For medicinal products for which a temporary emergency marketing authorisation may be considered by the Agency, Article 18(1) and (2) of Regulation (EU) 2022/123[36] shall apply.

   The Emergency Task Force shall provide a recommendation for a temporary emergency marketing authorisation to the Committee for Medicinal Products for Human Use for an opinion in accordance with Article 32. To this purpose, the Emergency Task Force set up pursuant to Article 15 of Regulation (EU) 2022/123 may, where appropriate, perform the activities referred to in Article 18(2) of that Regulation prior to the recognition of a public health emergency.

[36] Regulation (EU) 2022/123 of the European Parliament and of the Council of 25 January 2022 on a reinforced role for the European Medicines Agency in crisis preparedness and management for medicinal products and medical devices (OJ L 20, 31.1.2022, p. 1).

2. Where a request referred to in Article 18(3) of Regulation (EU) 2022/123 for a recommendation has been made and there is an application for a temporary emergency marketing authorisation for the medicinal product concerned, the procedure for a recommendation under Article 18(3) of Regulation (EU) 2022/123 shall be stopped and the procedure for a temporary emergency marketing authorisation shall prevail. Any available data shall be considered under the temporary emergency marketing authorisation application.

~~*Article 39*~~

~~*Withdrawal of authorisations granted in accordance with Article 3(2) of [revised Directive 2001/83/EC]*~~

~~When the Commission has granted a temporary emergency marketing authorisation in accordance with Article 33, Member States shall withdraw any authorisation granted in accordance with Article 3(2) of [revised Directive 2001/83/EC] for the use of medicinal products containing the same active substance for any indications that are subject to the temporary marketing authorisation.~~

REVISED DIRECTIVE

Article 4

Definitions

(51) 'public health emergency' means a public health emergency recognised at Union level by the Commission under Article 23(1) of Regulation (EU) 2022/2371 of the European Parliament and of the Council[37];

[37] 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).

2ND READING PACKAGE:

REGULATORY PROTECTION, INNOVATION, UMN (Incentives)

RECITALS

REVISED DIRECTIVE

(2) The most recent comprehensive revision took place between 2001 and 2004 while targeted revisions on post-authorisation monitoring (pharmacovigilance) and on falsified medicines 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. Moreover, some patients may not benefit from innovation because medicines may be unaffordable or not placed on the market in the Member State concerned. There is also a greater awareness of the environmental impact of medicines. More recently, the COVID-19 pandemic has stress tested the framework.

(3) This revision is part of the implementation of the Pharmaceutical strategy for Europe and aims to promote innovation, in particular for unmet medical needs, while reducing regulatory burden and the environmental impact of medicines; ensure access to innovative and established medicines 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 keeps medicines affordable for health systems while rewarding innovation.

(11) The Directive should work in synergy with the Regulation to enable innovation and promote competitiveness of the Union pharmaceutical industry, in particular SMEs. In this respect a balanced system of incentives is proposed that rewards innovation especially in areas of unmet medical need and innovation that reaches patients and improves access across the Union. To make the regulatory system more efficient and innovation-friendly the Directive also aims at reducing administrative burden and simplifying procedures for undertakings.

(23) As market forces alone have proven insufficient to stimulate adequate research into, and the development and authorisation of, medicinal products for the paediatric population, a system of both obligations and rewards and incentives has been put in place.

(26) In order to reward the compliance with all the measures included in the agreed paediatric investigation plan, for products covered by a supplementary protection certificate, if relevant information on the results of the studies conducted is included in the product information, a reward should be granted in the form of a six month extension of the supplementary protection certificate created by [Regulation (EC) No 469/2009 of the European Parliament and of the Council[38]- OP please replace reference by new instrument when adopted].

(44) 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 authorisation for medicinal products for unmet medical need. While these measures accelerated the authorisation of innovative and promising therapies, these 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 may decide not to market their medicinal products in, or withdraw them from, one or more Member States. 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.

[38] 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. 10).

(45) Addressing unequal patient access and affordability of medicinal products has become a key priority of the Pharmaceutical Strategy for Europe, as also highlighted by Council conclusions[39] and a resolution of the European Parliament[40]. Member States called for revised mechanisms and incentives for development of medicinal products tailored to the level of unmet medical need, while ensuring health system sustainability, patient access and availability of affordable medicinal products in all Member States.

(46) Access also comprise 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 and biosimilar medicinal products. The competition from generic and biosimilar medicinal products should also, in turn, increase patient access to medicinal products.

(47) To ensure dialogue among all actors in the medicines lifecycle, discussions on policy issues related to the application of the rules related to prolongation of regulatory data protection for market launch shall take place in the Pharmaceutical Committee. The Commission may invite bodies responsible for health technology assessment as referred to in Regulation (EU) 2021/2282 or national bodies responsible for pricing and reimbursement, as required, to participate in the deliberations of the Pharmaceutical Committee.

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[39] Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States, (OJ C, C/269, 23.07.2016, p. 31). Council Conclusions on Access to medicines and medical devices for a Stronger and Resilient EU, (2021/C 269 I/02).

[40] European Parliament resolution of 2 March 2017 on EU options for improving access to medicine (2016/2057(INI)) Shortages of medicines, 2020/2071(INI).

(48) 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 medicines 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 medicines, while fully respecting the competences of Member States in this area. The Commission may also 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 incentive.

(49) Joint procurement, whether within a country or across countries, can improve access, affordability, and security of supply of medicines, in particular for smaller countries. Member States interested in joint procurement of medicines can make use of Directive 2014/24/EU[41], which sets out purchasing procedures for public buyers, the Joint Procurement Agreement[42] and the proposed revised Financial Regulation[43]. Upon request from the Member States the Commission may support interested Member States by facilitating coordination to enable access to medicines for patients in the Union as well as information exchange, in particular for medicines for rare and chronic diseases.

[41] 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).
[42] 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.
[43] COM/2022/223 final.

(50) The establishment of a criteria-based definition of 'unmet medical need' is required 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 Commission should specify and update using implementing acts, the criteria of satisfactory method of diagnosis, prevention or treatment, 'remaining high morbidity or mortality', 'relevant patient population' following scientific assessment by the Agency. The Agency will 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 the [revised Regulation (EC) No 726/2004] and also take into account scientific initiatives at EU level or between Member States related to analysing unmet medical needs, burden of disease and priority setting for research and development. The criteria for 'unmet medical need' can be subsequently used by Member States to identify specific therapeutic areas of interest.

(51) The inclusion of new therapeutic indications to an authorised medicinal products contributes to the access of patients to additional therapies and therefore should be incentivised.

(52) For the initial marketing authorisation application for medicinal products containing a new active substance, the submission of clinical trials that include as a comparator an evidence-based existing treatment should be incentivised, in order to foster the generation of comparative clinical evidence that is relevant and can accordingly support subsequent health technology assessments and decisions on pricing and reimbursement by Member States.

(53) A marketing authorisation holder should ensure the appropriate and continuous supply of a medicinal product throughout its lifetime irrespective of whether that medicinal product is covered by a supply incentive or not.

(54) Micro, small and medium-sized enterprises ('SMEs'), not-for-profit entities or entities with limited experience in the Union system should benefit from additional time to market a medicinal product in the Member States where the marketing authorisation is valid for the purposes of receiving additional regulatory data protection.

(55) When applying the provisions on market launch incentives, 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 or hindering the other party from enjoying its rights under this Directive.

(56) Member States have the possibility to waive the condition of launch in their territory for the purpose of the prolongation of data protection for market launch. This can be done through a statement of non-objection to prolong the period of regulatory data protection. This is expected to be the case particularly in situations where launch in a particular Member State is materially impossible or because there are special reasons why a Member State wishes that launch take place later.

(57) The issuing of documentation from the Member States as regards the prolongation of data protection for the purpose of supply of medicinal products in all Member States where a marketing authorisation is valid, in particular the waiver to the conditions for such prolongation, does not affect at any time the powers of the Member States as regards the supply, setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes. Member States do not waive the possibility to request release or supply of the product concerned at any time before, during or after the prolongation of the data protection period.

(58) An alternative way of demonstrating supply relates to the inclusion of medicinal products in a positive list of medicinal products covered by the national health insurance system in accordance with Directive 89/105/EEC. The related negotiations between companies and the Member State should be conducted in good faith.

(59) A Member State that considers that the conditions of supply have not been met for its territory should provide a reasoned statement of non-compliance at the latest in the Standing Committee on Medicinal Products for Human Use procedure of the variation linked to the provision of the relevant incentive.

(60) The Commission and Member States shall continuously monitor any data and learnings from the application of the incentives system in order to improve, including through implementing acts, how these provisions are applied. The Commission shall establish a list of national contact points in this regard.

(61) When a compulsory licence has been granted by a relevant authority in the Union to tackle a public health emergency, regulatory data protection may, if still in force, prevent the effective use of the compulsory licence as they impede the authorisation of generic medicinal products, and thus access to the medicinal products needed to address the crisis. For this reason, data and market protection should be suspended when a compulsory licence has been issued to tackle a public health emergency. Such a suspension of the regulatory data protection should be allowed only in relation to the compulsory licence granted and its beneficiary. The suspension shall comply with the objective, the territorial scope, the duration and the subject matter of the granted compulsory licence.

(62) The suspension of the regulatory data protection should be granted only for the duration of the compulsory licence. A ‘suspension‘ of data and market protection in cases of public health emergency shall mean that data and market protection shall 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 data and market protection shall resume their effect. The suspension should not result in an extension of the original duration.

(63) It is currently possible for applicants for marketing authorisation of generic, biosimilar, hybrid and bio-hybrid medicinal products to conduct studies, trials and 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 (SPC) of the reference medicinal product, without this being considered patent or SPC infringement. The application of this limited exemption 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 that rely on a reference medicinal product, to clarify its scope in order to ensure a harmonised application in all Member States, both in terms of beneficiaries and in terms of activities covered. The exemption must be confined to conduct studies and trials and other activities needed for the regulatory approval process, health technology assessment and pricing reimbursement request, even though this may require substantial amounts of test production to demonstrate reliable manufacturing. During the term of protection of the patent or SPC of the reference medicinal product, there can be no commercial use of the resulting final medicinal products obtained for the purposes of the regulatory approval process**, even in the cases of procurement tenders**.

(64) It will allow, inter alia, to conduct studies to support pricing and reimbursement as well as the manufacture or purchase of patent protected active substances for the purpose of seeking marketing authorisations during that period, contributing to the market entry of generics and biosimilars on day one of loss of the patent or SPC protection.

(65) The competent authorities should refuse the validation for an application for a marketing authorisation 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 the marketing authorisation. The competent authorities cannot base their decision on any other grounds. In particular, those decisions cannot be based on the patent or SPC status of the reference medicinal product. **~~While this corresponds to the current application of the regulatory framework of medicinal products, it seems appropriate to clarify it in this Directive for the avoidance of doubt. Similarly, the protection of intellectual property rights shall not be a valid ground to refuse or suspend decisions related to pricing and reimbursement or health technology assessment procedures.~~ From these rules it also stems that the protection of intellectual property rights does not represent a valid ground to refuse or suspend decisions related to relevant pricing and reimbursement or health technology assessment procedures.~~However.~~ Member States ~~should~~ remain free to introduce ~~a national requirement~~ rules to ~~prove~~ ensure the ~~availability~~ readiness to supply ~~of~~ a ~~medicine~~ medicinal product on the market of that Member State for the period when the patent and SPC ~~has~~ have expired~~at the date of submission of the application for pricing and reimbursement.~~**

(90) 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 from biological medicinal products to biosimilars or advanced therapy medicinal products or in the future phages therapies. Those categories of products may 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 European Medicines Agency.

(91) The adaptations may entail adapted, enhanced, waived or deferred 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 practices requirements, as well as additional control methods prior and during their administration and use. The adaptions should however not go beyond what is necessary for the attainment of the objective of adaptation to the specific characteristics.

(120) 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 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.

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

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(19) Scientific advice for future applicants seeking a marketing authorisation should be provided more generally and in greater depth. Similarly, structures allowing the development of advice for companies, in particular small and medium-sized enterprises (‘SMEs’), should be put in place.

(20) Promising medicinal products that have the potential to significantly address patients' unmet medical needs should benefit from early and enhanced scientific support. Such support will ultimately help patients benefit from new therapies as early as possible.

(45) Marketing authorisation applications, like any other application submitted to the Agency, should follow the digital by default principle and hence be sent to the Agency in electronic form. Applications should be assessed based on the file submitted by the applicant in accordance with the different legal basis provided by [revised Directive 2001/83/EC]. At the same time, the Agency and the relevant committees may take into account any information that is in its possession. Applicants shall be requested to generally submit raw data, in particular with regard to the clinical trials performed by the applicant in order to ensure a full assessment of the quality, safety and efficacy of the medicinal product.

(55) For medicinal products, the period for protection of data relating to non-clinical tests and clinical trials should be the same as that provided for in [revised Directive 2001/83/EC].

(77) The development of antimicrobial resistance is a growing concern and the pipeline of effective antimicrobials is obstructed due to a market failure; it is therefore necessary to consider new measures to promote the development of priority antimicrobials that are effective against antimicrobial resistance and to support undertakings, often SMEs, which choose to invest in this area.

(79) The creation of a voucher rewarding the development of priority antimicrobials through an additional year of regulatory data protection has the capacity to provide the needed financial support to developers of priority antimicrobials. However, in order to ensure that the financial reward which is ultimately borne by health systems is mostly absorbed by the developer of the priority antimicrobial and not the buyer of the voucher, the number of available vouchers on the market should be kept to a minimum. It is therefore necessary to establish strict conditions of granting, transfer and use of the voucher and to further give the possibility to the Commission to revoke the voucher under certain circumstances.

(99) A vast percentage of rare diseases remains without treatment with research and development clustered in the areas where profit is better assured. Therefore, there is a need to target those areas where research is mostly needed and where investments are most risky.

(100) Orphan medicinal products addressing a high unmet medical need prevent, diagnose or treat conditions where either no other method of prevention, diagnosis or treatment exists or, if such method already exists, they would bring exceptional therapeutic advancement. In both cases, the criterion of meaningful reduction in disease morbidity or mortality for the relevant patient population should ensure that only most effective medicinal products are covered. The Agency should draw up scientific guidelines on the category of 'orphan medicinal products addressing a high unmet medical need'.

(101) Experience since the adoption of Regulation (EC) No 141/2000 shows that the strongest incentive for industry to invest in the development and making available of orphan medicinal products is where there is a prospect of obtaining market exclusivity for a certain number of years during which part of the investment might be recovered. In addition to the periods of market exclusivity, orphan medicinal products will benefit from the periods of regulatory protection set out in [revised Directive 2001/83/EC], including the prolongations of regulatory data protection. However, where an orphan medicinal product obtains an additional therapeutic indication it will benefit only from the prolongation of market exclusivity.

(102) In order to incentivise research and development of orphan medicinal products addressing high unmet needs, to ensure market predictability and to ensure a fair distribution of incentives, a modulation of market exclusivity has been introduced; orphan medicinal products addressing high unmet medical needs benefit from the longest market exclusivity, while market exclusivity for well-established use orphan medicinal products, requiring less investment, is the shortest. In order to ensure increased predictability for developers, the possibility to review the eligibility criteria for market exclusivity after six years after the marketing authorisation has been abolished.

(103) In order to encourage faster and wider access also to orphan medicinal products, an additional period of one year of market exclusivity is granted to orphan medicinal products for a Union market launch, with the exception of well-established use medicinal products.

(104) To reward research into and development of new therapeutic indications, an additional period of one year of market exclusivity is provided for a new therapeutic indication (with a maximum of two indications).

(133) Regulatory sandboxes can provide the opportunity for advancing regulation through proactive regulatory learning, enabling regulators to gain better regulatory knowledge and to find the best means to regulate innovations based on real-world evidence, especially at a very early stage of development of a medicinal product, which can be particularly important in the face of high uncertainty and disruptive challenges, as well as when preparing new policies. Regulatory sandboxes provide a structured context for experimentation, enable where appropriate in a real-world environment the testing of innovative technologies, products, services or approaches – at the moment especially in the context of digitalisation or the use of artificial intelligence and machine learning in the life cycle of medicinal products from drug discovery, development to the administration of medicinal products – for a limited time and in a limited part of a sector or area under regulatory supervision ensuring that appropriate safeguards are in place. In its conclusions of 23 December 2020 the Council has encouraged the Commission to consider the use of regulatory sandboxes on a case-by-case basis when drafting and reviewing legislation.

(134) In the area of medicinal products, a high level of protection of inter alia citizens, consumers, health, as well as legal certainty, a level playing field and fair competition always need to be ensured and existing levels of protection need to be respected.

(135) The establishment of a regulatory sandbox should be based on a Commission **implementing** Decision, ~~following a recommendation of~~ **after having consulted** the Agency. Such decision should be based on a detailed plan outlining the particularities of the sandbox as well as describing the products to be covered. A regulatory sandbox should be limited in duration and ~~may~~**could** be terminated at any time based on public health considerations. The learning stemming from a regulatory sandbox **are capable of** ~~should~~ inform**ing** future changes to the legal framework **in order** to fully integrate the particular innovative aspects into the medicinal product regulation. Where appropriate, adapted frameworks ~~may~~**could** be developed by the Commission on the basis of the results of a regulatory sandbox. **Marketing Authorisations under a sandbox should be granted on the basis of the same regulatory principles of quality, safety and efficacy as other medicinal products. The regulatory sandbox should not affect the supervisory and corrective powers of the competent authorities and the liability of the participants, such as clinical trial sponsors, marketing authorision holders, applicants for marketing authorisation, or any entities involved in the lifecycle of the medicinal product**.

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ADAPTED FRAMEWORKS

Chapter II

Application requirements for national and centralised marketing authorisations

Section 5

Adapted dossier requirements

Article 28

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

1. Medicinal products **or category of medicinal products** listed in Annex VII shall be subject to **adapted** ~~specific~~ scientific or regulatory requirements **('adapted framework')** due to the characteristics or methods inherent to the medicinal product **or category of medicinal products**~~.~~**. A medicinal product or category of medicinal products shall be listed in Annex VII** when:
   (a) it is not possible to adequately assess the medicinal product or category of medicinal products applying the applicable requirements **set out in this Directive, the [revised Regulation (EC) No 726/2004] or Regulation 1394/2007** due to scientific or regulatory challenges arising from **objective and scientific** characteristics or methods inherent to the medicinal product **or category of medicinal products**; and
   (b) the characteristics or methods **inherent to the medicinal product or category of medicinal products** positively impact the quality, safety and efficacy of the medicinal product or category of medicinal product or provide a major contribution to patient access **to prevention, diagnosis, ~~or~~ treatment** or **~~any other form of~~** patient care.

2. **~~Based on a recommendation by~~ After having consulted the Agency, t**~~T~~he Commission is empowered to adopt delegated acts in accordance with Article 215 to amend **the list of medicinal products or categories of medicinal products listed in ~~the list of areas of adapted frameworks under~~** Annex VII in order to take account of scientific and technical progress.

3. The Commission **~~may adopt implementing acts~~** is empowered**, after having consulted the Agency,** to adopt delegated ~~**implementing**~~ acts in accordance with Article 215 ~~**214** to supplement this Directive~~ by laying down **the adapted framework for one or more medicinal products or categories of medicinal produts listed in Annex VII.**

The adapted framework may entail ~~adapted, enhanced, waived or deferred~~ targeted adaptations to the requirements set out in this Directive. The adapted ~~framework~~ requirements shall be proportionate to the risk and impact involved and based on objective and scientific considerations. In particular, any waiver or deferral from the ~~standards of~~ requirements shall entail equivalent standards of ~~for~~ quality, safety and efficacy to those set out in this Directive and shall be limited to the extent strictly necessary, proportionate and duly justified by the characteristics or methods inherent to the medicinal product or category of medicinal products~~.~~. The waivers or deferrals ~~and~~ shall be regularly reviewed and evaluated by the Commission. Apart from the detailed rules set out in the delegated act, all other rules laid out in this Directive shall apply. The delegated act shall also contain the technical documentation to be submitted by marketing authorisation applicants for the medicinal product or category of medicinal products for which the adapted framework is laid down. ~~:~~

~~(a) **specific** detailed rules for the marketing authorisation and supervision of the medicinal products **or category of medicinal products** referred **pursuant** to **the criteria referred to** in paragraph 1;~~

~~(b) the technical documentation to be submitted by applicants for marketing authorisations for medicinal products referred to in paragraph 1.~~

~~Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 214(2).~~

~~3a. The Commission is empowered, after consulting the Agency and when it deems that the conditions set out in paragraph 1 are met, to adopt a delegated act in accordance with Article 215 to specify, for each of the medicinal products or category of medicinal products listed in Annex VII, the list of specific scientific or regulatory requirements applicable to that medicinal product or category of medicinal products. The specific applicable requirements shall be proportionate to the risk and impact involved.~~

4. **~~The Commission shall, taking into account a scientific assessment by the Agency, specify whether those requirements entail an adaptation, enhancement, waiver or deferral from the requirements laid down in this Directive, the [revised Regulation (EC) No 726/2004] or Regulation 1394/2007.~~** ~~The **specific** detailed rules referred to in paragraph 3, point (a), shall be proportionate to the risk and impact involved. These may entail adapted, enhanced, waived or deferred requirements. Any **adaptation, enhancement,** waiver or deferral shall be limited to the extent strictly necessary, proportionate and duly justified by the characteristics or methods inherent to the medicinal product **or category of medicinal products**, and shall be regularly reviewed and evaluated **by the Commission** **by the Agency**. Apart from the **specific** detailed rules referred to in paragraph 3, point (a), all other rules laid out in this Directive shall apply.~~

5. Until the adoption of **specific** **adapted** ~~detailed rules~~ **requirements** for ~~specific~~ medicinal products **or category of medicinal products** listed in Annex VII pursuant to paragraph 3, an application for a marketing authorisation for that medicinal product may be submitted in accordance with Article 6(2).

6. When adopting **~~implementing and~~** delegated acts **~~or implementing 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 115 of the [revised Regulation (EC) No 726/2004].

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Article 6

Centralised marketing authorisation application

(…)

8. Adapted frameworks established in accordance with Article 28 of [revised Directive 2001/83] shall apply to centralised marketing authorisations. Those adapted frameworks may entail adapted, enhanced, waived or deferred requirements to the Regulation, as specified in the delegated acts adopted in accordance with Article 28(3) of [revised Directive 2001/83/EC].

Article 176

Amendments to Regulation (EC) No 1394/2007

Regulation (EC) No 1394/2007 is amended as follows:

(…)

(3) the following Article 7a is inserted:

'Article 7a

Adapted frameworks for ATMPs

Adapted frameworks established in accordance with Article 28 of [revised Directive 2001/83] shall apply to centralised marketing authorisations. Those adapted frameworks may entail adapted, enhanced, waived or deferred requirements to the Regulation, as specified in the delegated acts adopted in accordance with Article 28(3) of [revised Directive 2001/83/EC].'

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REGULATORY DATA PROTECTION, UNMET MEDICAL NEEDS, REWARDS FOR PAEDIATRICS

Chapter VII

Regulatory protection, unmet medical needs and rewards for paediatric medicinal products

Article 80

Regulatory data and market protection

1. The data referred to in Annex I, originally submitted with the view to obtaining a marketing authorisation shall not be referred to by another applicant for a subsequent marketing authorisation during the period determined in accordance with Article 81 ('regulatory data protection period').

2. A medicinal product concerned by a subsequent marketing authorisation referred to in paragraph 1 shall not be placed on the market for a period of two years after the expiry of the relevant regulatory data protection periods referred to in Article 81.

The period shall be extended to three years if, during the regulatory data protection period referred to in paragraph 1, the marketing authorisation holder ~~concerned~~ 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. ~~When applying for an extension under this subparagraph and where such data were not available when the applicant shall demonstrates that the clinical study reports results of the clinical trials specific to the approval of the new indication were not available at the time of the submission of the initial authorisation application initial marketing authorisation was submitted.~~

3. By way of derogation from paragraph 1, the marketing authorisation holder concerned may grant the marketing authorisation applicant for another marketing authorisation a letter of access to its data submitted under Annex I, as referred to in Article 14.

4. By way of derogation from the paragraphs 1 and 2, when a compulsory licence has been granted by a relevant authority in the Union to a ~~party~~ **licensee** **under conditions laid out in Union or national law** ~~to address a public health emergency~~, the **relevant** data and market protection shall be suspended with regard to that ~~party~~ **licensee** insofar as the compulsory licence requires, ~~and during~~ **for** the duration **and the territory of the Member States for which** ~~period of~~ the compulsory licence **has been granted**.

5. The data protection period set out to in paragraph 1 shall also apply in Member States where the medicinal product is not authorised or is no longer authorised.

5a. National competent authorities shall make on their website available the list of medicinal products they have granted a national marketing authorisation and are protected by regulatory data ~~or market~~ protection, ~~together with the date of the end of the protection period,~~indicating the applicable prolongation in accordance with Article 81. The Agency shall compile and publish a list of hyperlinks to the websites referred to in this paragraph.

~~5a. The marketing authorisation holder The Agency shall include submit and keep up to date the information on data and market protection periods for both centrally authorised medicinal products and medicinal products that have been granted a national marketing authorisation in the database referred to in Article 138 paragraph 1, point (n) of the [revised Regulation (EC) No 726/2004].[44] The marketing authorisation holder shall notify the Agency with supporting documentation whenever the information published concerning the relevant regulatory and market protection periods is missing, not accurate or outdated.~~

~~5b. In case of medicinal products covered by a national marketing authorisation, the national competent authorities that granted the authorisation shall be informed through the database without delay on any submissions and updates made in accordance with paragraph 5a. If the National competent authority does not inform the Agency on its objection within 8 30 days, the data shall be published in the database. In case of objection, the national competent authority shall invite without undue delay the marketing authorisation holder to make a correct submission. Until a new submission is not made and approved under this paragraph, the data related to data and market protection periods indicated in the database shall remain unchanged.~~

Article 81

Regulatory data protection periods

1. The regulatory data protection period shall be ~~six~~ **seven ~~eight~~** years from the date when the marketing authorisation for that medicinal product was granted in accordance with Article 6(2). For marketing authorisations that belong to the same global marketing authorisation the period of data protection shall start from the date when the initial marketing authorisation was granted in the Union.

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[44] ~~*Presidency note: In order to be coherent, it should be specified in Article 16 of the Regulation (on 'marketing authorisations') that this information on data and market protection periods should be integrated into the register referred to in Article 138. However, as this Article is a central Article in the 'authorisations cluster', we decided not to add it to this cluster.*~~

2. ~~Subject to a scientific evaluation by the relevant competent authority, the data protection period referred to in paragraph 1 shall be prolonged by:~~ **~~The data protection period referred to in paragraph 1 shall be prolonged by:~~ ~~By way of derogation from paragraph (1) the data protection period shall be 7 years if none of the following conditions is fulfilled~~:**

~~(a) 24 months, where the marketing authorisation holder demonstrates that the conditions referred to in Article 82(1) are fulfilled within two years, from the date when the marketing authorisation was granted or, within three years from that date for any of the following entities:~~

~~(i) SMEs within the meaning of Commission Recommendation 2003/361/EC;~~

~~(ii) entities not engaged in an economic activity ('not-for-profit entity'); and~~

~~(iii) undertakings that, by the time of granting of a marketing authorisation, have received not more than five centralised marketing authorisations for the undertaking concerned or, in the case of an undertaking belonging to a group, for the group of which it is part, since the establishment of the undertaking or the group, whichever is earliest.~~

The regulatory data protection period referred to in paragraph 1 shall be prolonged by the following periods ~~not exceeding 8 year in total~~ by:

(a) 12 months, where the marketing authorisation applicant demonstrates at the time of the initial marketing authorisation application that the medicinal product addresses an unmet medical need as referred to in Article 83;

or

(b) 12 ~~6~~ months for medicinal products containing a new active substance, where the marketing authorisation applicant demonstrates the fulfillment of all ~~if they meet all of~~ the following conditions:

i) ~~where appropriate, where~~ the clinical trials supporting the initial marketing authorisation application use, where possible and appropriate, a relevant and evidence-based comparator in accordance with the scientific advice provided by the Agency;

~~(c) ii) 12 6 months where the marketing authorisation holder demonstrates that a significant share of research and development, including preclinical and clinical studies, related to the medicinal product has been done within the Union and at least partly in collaboration with public entities, including university hospital institutes health centres, centres of excellence or bioclusters located in the Union. the marketing authorisation applicant carried out~~ **clinical trials evaluating the efficacy of the medicinal product and used for the marketing authorisation were conducted in ~~at least two~~ several Member States ~~of the European Union~~.**

~~(d) 6 months where the marketing authorisation holder demonstrates that the medicinal product or the active substance was manufactured in the European Union, excluding import related processes.~~

~~(e) iii) 6 months if~~ the marketing authorisation applicant ~~holder~~ demonstrates that the ~~application for granting~~ marketing authorisation application has been first submitted to the competent authority in the Union or has been submitted no later than 90 days after the submission of the application for the first marketing authorisation outside the Union.

In the case of prolongation of data protection in accordance with paragraph 2(a), the applicant shall demonstrate the improvement in efficacy or safety of the medicinal product referred to in Article 83 paragraph 1(b) with data from clinical trials that use, where possible and appropriate, a relevant and evidence-based comparator.

~~**The cumulative duration of data protection for a medicinal product shall not exceed eight years from the date the initial marketing authorisation was granted.**~~

In the case of a conditional marketing authorisation granted in accordance with Article 19 of [revised Regulation (EC) No 726/2004] the prolongation ~~**condition**~~ referred to in the first subparagraph, point (~~**b**~~**a**), shall only apply ~~**be considered as met**~~ 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 19(7) of [revised Regulation (EC) No 726/2004**, and;**~~.~~

- **in the case of medicinal products referred to in Article 83, paragraph 1(b), the studies referred to in Article 19(4) of [revised Regulation (EC) No 726/2004] shall include clinical trials that use, where possible and appropriate, a relevant and evidence-based comparator.**

~~The prolongation referred to in the first subparagraph, point (d), may only be granted once.~~ **~~The cumulative duration of data protection for a medicinal product shall not exceed eight years from the date the initial marketing authorisation was granted. [This limitation does not apply in the case of Article 40 of [revised Regulation (EC) No 726/2004].]~~**

The cumulative duration of data protection for a medicinal product shall not exceed eight years from the date when the initial marketing authorisation was granted, except when one additional year of data protection is granted in accordance with Article 41 (1).

3. The Agency shall set the scientific guidelines referred to in paragraph 2, point (~~c~~**b**) **(i)** ~~**(iii)**~~, on criteria for proposing a comparator for a clinical trial, taking into account the results of the consultation of the Commission and the authorities or bodies involved in the mechanism of consultation referred to in Article 162 of [revised Regulation (EC) No 726/2004]**, in particular bodies responsible for health technology assessment as referred to in Regulation (EU) 2021/2282**.

~~4. The Commission is empowered to adopt delegated acts in accordance with Article 215 to supplement paragraph 2 point (ba) c in order to determine situations in which a set specific criteria for the designation of significant substantial share of research and development is done within the Union.~~

Article 82

Prolongation of the data protection period for medicinal products supplied in Member States

1. The prolongation of the data protection period referred to in Article 81(2), first subparagraph, point (a), shall only be granted to medicinal products if they are released and continuously supplied into the supply chain in a sufficient quantity and in the presentations necessary to cover the needs of the patients in the Member States in which the marketing authorisation is valid.

The prolongation referred to in the first subparagraph shall apply to medicinal products that have been granted a centralised marketing authorisation, as referred to in Article 5 or that have been granted a national marketing authorisation through the decentralised procedure, as referred to in Chapter III, Section 3.

2. To receive a prolongation referred to in Article 81(2), first subparagraph, point (a), the marketing authorisation holder shall apply for a variation of the relevant marketing authorisation.

The application for a variation shall be submitted between 34 and 36 months after the date when the initial marketing authorisation was granted, or for entities referred to in Article 81(2), first subparagraph, point (a), between 46 and 48 months, after that date.

The application for a variation shall contain documentation from the Member States in which the marketing authorisation is valid. Such documentation shall:

(a) confirm that the conditions set out in paragraph 1 have been satisfied in their territory; or

(b) waive the conditions set out in paragraph 1 in their territory for the purpose of the prolongation.

Positive decisions adopted in accordance with Articles 2 and 6 of Council Directive 89/105/EEC[45] shall be considered equivalent to a confirmation referred to in the third subparagraph, point (a).

3. To receive the documentation referred to in paragraph 2, third subparagraph, the marketing authorisation holder shall make a request to the relevant Member State. Within 60 days from the request of the marketing authorisation holder, the Member State shall issue a confirmation of compliance or, a reasoned statement of non-compliance or alternatively provide a statement of non-objection to prolong the period of regulatory data protection pursuant to this Article.

4. In cases where a Member State has not replied to the application of the marketing authorisation holder within the deadline referred to in paragraph 3, it shall be considered that a statement of non-objection has been provided.

For medicinal products granted a centralised marketing authorisation the Commission shall vary the marketing authorisation pursuant to Article 47 of [revised Regulation (EC) No 726/2004] to prolong the data protection period. For medicinal products granted a marketing authorisation in accordance with the decentralised procedure, the competent authorities of the Member States shall vary the marketing authorisation pursuant to Article 92 to prolong the data protection period.

5. 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[46] ('Pharmaceutical Committee'). The Commission may invite bodies responsible for health technology assessment as referred to in Regulation (EU) 2021/2282 or national bodies responsible for pricing and reimbursement, as required, to participate in the deliberations of the Pharmaceutical Committee.

[45] Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems (OJ L 40, 11.2.1989, p. 8).

[46] Council Decision of 20 May 1975 setting up a pharmaceutical committee (OJ L 147, 9.6.1975, p. 23).

~~6. The Commission, based on the experience of Member States and relevant stakeholders, may adopt implementing measures relating to the procedural aspects outlined in this Article and regarding the conditions mentioned in paragraph 1. Those implementing acts shall be adopted in accordance with the procedure referred to in Article 214(2).~~

Chapter V

Obligations and liability of the marketing authorisation holder

Article 56a

Specific requirements ~~Obligation to~~ on making available ~~market launch~~ and ~~continuously~~ supplying of a medicinal product ~~on the market~~ in a Member State

1. With a view to facilitating access to a medicinal product covered by a valid marketing authorisation within the~~ir~~ territory~~ies~~ of a Member State subject to regulatory protection pursuant to Article 80~~(2)~~, or, if applicable, the ~~prolongation of the~~ market exclusivity in accordance with Article 72~~(2)~~ of [revised Regulation 726/2004], a Member State may request the marketing authorisation holder of that medicinal product to make it available and ~~continuously~~ supply, ~~within the limits of its responsibility~~, on the market of that Member State in ~~a~~ sufficient quantities and in the presentations necessary to cover the needs of patients in that Member State, as specified by that Member State.

2. For the purposes of paragraph 1, a Member State may require the marketing authorisation holder to carry out specific actions pursuant to national law, including but not limited to, the following:

a) submit a valid~~meeting procedural obligations on marketing authorisation holders for~~ pricing and reimbursement application;

b) fulfilling specific requirements for marketing authorisation holders in procurement procedures;

c) establishing a~~n access~~ roll-out ~~supply~~ plan.

~~Such~~ The arrangements to implement the requirements referred to in this paragraph shall be proportionate to the objective pursued and in compliance with Union law.

~~2a. Upon request by a Member State in accordance with paragraph 1, the marketing authorisation holder concerned shall carry out the actions referred to in paragraph 2 as relevant.~~

3. The ~~supply access~~ roll-out plan referred to in paragraph 2, point (c), 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 ~~supply access~~ roll-out plan shall be prepared by the marketing authorisation holder and be agreed by the Member State concerned. The Member State may require the marketing authorisation holder to update the ~~supply access~~ roll-out plan.

4. When a Member State ~~decides to avail itself of the obligation in~~ applies paragraph 1, it shall communicate it to the marketing authorisation holder, together with the modalities referred to in paragraph 2, within one year from the marketing authorisation for that medicinal product. The communication under this paragraph shall contain explicit reference to this Article.

5. Where within ~~5~~ 4 years after the marketing authorisation of the medicinal product has been granted, the marketing authorisation holder has not made the medicinal product available and has not supplied it continuously within that period in ~~a~~ sufficient quantities and in the presentations necessary to cover the needs of patients in a Member State that made a request in accordance with paragraph 1, the market protection for that medicinal product in accordance with Article 80(2), and, if applicable, the prolongation of the market exclusivity in accordance with Article 72(2) of [revised Regulation 726/2004] shall not apply within that Member State.

5a. The Member State shall make the information referred to in paragraph 5 publicly available without undue delay. For medicinal products authorised in accordance with [revised Regulation (EC) No 726/2004] the Member State shall also notify the Agency.

5b~~a~~. By way of derogation from Article 81, a marketing authorisation application may be validated and assessed by the national competent authorities or the Agency six years after the start of the data protection period of the reference medicinal product, where the medicinal product is a generic or biosimilar medicinal product to a reference medicinal product and where a Member State has made publicly available information with regard to that reference medicinal product in accordance with paragraph 6. The marketing authorisation validated and assessed in accordance with this paragraph shall not be granted prior to the expiry of the regulatory data protection period.

~~6. The Member State shall make this the information referred to in paragraph 5 publicly available without undue delay. For medicinal products authorised in accordance with [revised Regulation (EC) No 726/2004] the Member State shall also notify the Agency.~~

7. This Article shall not affect ~~is without prejudice to Member States'~~ the application of national legislation and procedures, including pricing and reimbursment, public procurement and any other procedures, aiming at making available and ~~continuously~~ supplying the medicinal product concerned within their territory at any time following the marketing authorisation~~, where a request in accordance with paragraph 1 has been made by that Member State~~.

This Article shall also not affect the right of marketing authorisation holders to ~~release~~ make available and ~~continuously~~ supply the medicinal product concerned in a Member State by carrying out the relevant procedures pursuant to national law, regardless of whether a request in accordance with paragraph 1 has been made by that Member State.

In the course of the application of this Article, the Member States and the marketing authorisation holder shall cooperate in good faith and undertake best efforts to making available and ~~continuously~~ suppling the medicinal product concerned in the concerned Member State.

8. 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[47] ('Pharmaceutical Committee'). The Commission may invite bodies responsible for health technology assessment as referred to in Regulation (EU) 2021/2282 or national bodies responsible for pricing and reimbursement, as required, to participate in the deliberations of the Pharmaceutical Committee.

The Pharmaceutical Committee may ~~coordinate~~ exchange views on national measures envisaged in the event when the obligations under this Article are not met ~~the notifications by the national competent authorities in agreement with Article 56b points 3 and 5~~.

Marketing authorisation holders shall comply with the obligations set out in this Article, except for exceptional and unforeseeable circumstances, including those related to disruptions of supply, outside the marketing authorisation holder's control, the consequences of which could not have been avoided even if all reasonable measures had been taken.

[47] **Council Decision of 20 May 1975 setting up a pharmaceutical committee (OJ L 147, 9.6.1975, p. 23).**

Recital:

Access to medicinal products in all Member States and guaranteeing a timely, stable, reliable and high-quality supply of medicinal products is an essential objective to achieve an overall high level 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~~n~~ timely, adequate and continuous supply of medicinal products so that to ensure 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 behaviour of marketing authorisation holders results in~~ the placing on the market of authorised medicinal products is delayed or 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 enabled to require to the MAHs specific actions with a view to comply with their market launch and supply obligations pursuant to this Directive. To this aim, Member States should be able to request the marketing authorisation holder to submit an application for pricing and reimbursement or to participate in any relevant national procurement procedures or ~~make the product available in the supply chain~~ draw up and implement a~~n access~~ roll-out plan that is acceptable for that Member State. The implementation of the ~~access~~ roll-out plan should ensure sufficient and continuous supply to meet the needs of the patients in that Member State. ~~Member States should base their request on the 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. Member States should also be able to request the submission and implementation of a supply plan that ensures sufficient and continuous supply to meet the needs of the patients in that Member State.~~

Article 166

Obligations of the wholesale distribution authorisation holder

5. **In respect of a medicinal product where the protection referred to in Article 80, paragraph (2) or the prolongation referred to in Article 72(2) of [revised Regulation 726/2004] does not apply in a Member State pursuant to Article 56a(5), the wholesale distribution holder shall not make the generic, biosimilar, hybrid and biohybrid medicinal product available on the market of another Member State where the protection referred to in Article 80 paragraph (2) and, if applicable, Article 72(2) of [revised Regulation 726/2004] applies, during the period of the protection.**

Article 216

Report

1. By [OP please insert the date = 10 years following 18 months after the date of entering 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.

2. **By [OP please insert the date = 6 years following ~~18 months after~~ the date of entering into force of this Directive], the Commission shall present a report ~~to the~~ to the European Parliament and the Council on the application of Article 56a. The report shall, based among others, on information provided by Member States, include an assessment whether the rules provided for in that Article ensures timely availability and continuous supply of medicinal products in a sufficient quantity in all Member States that have applied that Article. The Commission shall, if appropriate, present legislative proposals based on that evaluation in order to amend this Directive or make further proposals.**

Article 219

Transposition

1. Member States shall bring into force the laws, regulations and administrative provisions to comply with this Directive by [18 months after the date of entering into force of this Directive]. They shall immediately communicate the text of those measures to the Commission.

1a. Member States shall apply those measures from [18 months after the date of entering into force of this Directive].

However Member States may apply Article 56a from an earlier date in respect of medicinal products authorised after the date of entering into force of this Directive. In case of a medicinal product ~~authorised~~ which has been granted a marketing authorisation in accordance with Regulation 726/2004 or the Directive 2001/83 between the entry into force and the date of application of this Directive, the second subparagraph of Article 10 (1) of the Directive 2001/83 shall not apply in the member state that made a request in accordance with Article 56a, 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 that Article.

2. When Member States adopt those measures, they shall contain a reference to this Directive or 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.

3. 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.

Chapter XVI

General provisions

Article 206

Penalties

2. The rules referred to in paragraph 1, first subparagraph, shall address, inter alia, the following:
   (a) the manufacturing, distribution, brokering, import and export of falsified medicinal products, as well as sale at distance of falsified medicinal products to the public;
   (aa) non-compliance with the provisions laid down in this Directive on making available and ~~continuously~~ supply the medicinal product on the market of a Member State.
   (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.

REVISED REGULATION

Article 5

Submission of applications for marketing authorisations

[…]

1a. The marketing authorisation holder shall ensure that medicinal products authorised under this Regulation and which are subject, as applicable, to regulatory protection pursuant to Article 80, market exclusivity in accordance with Article 72 of [revised Regulation 726/2004], patent or a supplementary protection certificate, are made available and supplied for use in patients in all Member States, taking into account the relevant patient population, and requests and conditions for supply of the Member States to cover the needs of patients.

The marketing authorisation holder shall not be considered infringing this obligation, when it can demonstrate that non-compliance is due to exceptional and unforeseeable circumstances, including those related to disruptions of supply, outside the marketing authorisation holder's control.

(…)

ANNEX II

LIST OF THE OBLIGATIONS REFERRED TO IN ARTICLE 172

(…)

(8a) The obligation to make products available and supplied for use in patients in all Member States, as referred to in Article 5 (1a), in case of a consistent failure, based on submissions of non-accessibility from at least two Member States.

REVISED DIRECTIVE

Chapter VII

Regulatory protection, unmet medical needs and rewards for paediatric medicinal products

Article 83

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 ~~**satisfactory method of diagnosis, prevention or treatment in standard of care**~~ for such disease~~, or, where despite **the existence of a satisfactory method of diagnosis, prevention or treatment in standard of care** medicinal products being authorised for such disease in the Union, the disease is associated with a remaining high morbidity or mortality~~;

(b) the use of the medicinal product **for such a disease** results in **clinically relevant ~~advantage~~ improvement ~~a greater~~ in efficacy, or ~~greater~~ in safety with at least ~~non-inferior~~ comparable efficacy, in comparison with existing medicinal products or other methods of diagnosis, prevention or treatment authorised in the Union** ~~a meaningful reduction in disease morbidity or mortality for the relevant patient population. **The meaningful reduction in disease morbidity or mortality for the relevant patient population may shall be demonstrated, where possible and appropriate, with data from comparative clinical trials studies that use a relevant and evidence-based comparator in accordance with scientific advice provided by the Agency.**~~

~~**1a. The applicant shall demonstrate the improvement in efficacy or safety referred to in paragraph 1(b) with data from clinical trials that use, where possible and appropriate, a relevant and evidence-based comparator. In the case of paragraph 1(b), the applicant shall demonstrate the greater efficacy or safety with data from clinical trials that use a relevant and evidence-based comparators.**~~

~~2. Designated orphan medicinal products referred to in Article 67 of [revised Regulation (EC) No 726/2004] shall be considered as addressing an unmet medical need.~~

3. ~~Where t~~**T**he Agency **shall** adopt~~s~~ scientific guidelines ~~for~~ **to support** the application of this Article**. To this end,** it shall consult the Commission and the authorities or bodies referred to in Article 162 of [revised Regulation (EC) No 726/2004].

Article 84

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 ~~non-clinical~~ **and** ~~or~~ clinical studies **and, where relevant, non-clinical studies/tests** were carried out in relation to the therapeutic indication demonstrating that it is of significant clinical benefit, and

(b) the medicinal product is authorised in accordance with Articles 9 to 12**~~, with a different marketing authorisation holder than the reference medicinal product~~** and has not previously benefitted from data protection, or 25 years have passed since the granting of the initial marketing authorisation of the medicinal product concerned.

2. The data protection period referred to in paragraph 1 may only be granted once for any given medicinal product.

3. During the 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 85

Exemption to the protection of intellectual property rights

1. **The protection provided by p**~~P~~atent rights, or supplementary protection certificate~~s~~ **of medicinal products** ~~under the [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted]~~ shall not be regarded as infringed when **the necessary studies, trials and other activities are conducted** ~~**to generate the necessary data related to a**~~ reference ~~**patented product, or process, design or invention**~~ ~~medicinal product is used~~ for the purposes of:

~~(a) studies, trials and other activities conducted to generate data~~ **necessary** ~~for an application,~~ ~~**which are necessary**~~ ~~for:~~

(a)~~(i)~~ **obtaining** a marketing authorisation of **medicinal products, in particular of** generic, biosimilar, hybrid or bio-hybrid medicinal products and for subsequent variations;

(aa)~~(ii)~~ **conducting** health technology assessment as defined in Regulation (EU) 2021/2282;

(ab)~~(iii)~~ **obtaining** pricing and reimbursement **approval;**

(ac) complying with subsequent practical requirements associated with activities referred to in points (i)-(iii).

(ad)~~(aa)~~ submitting an application on procurement tenders ~~are submitted~~, in compliance with Union and national law, to the extent that it does not entail the sale or offering for sale of the marketing of the patented medicinal product during the protection period provided by patent rights or supplementary protection certificate.

~~(b)~~ **T**~~t~~he activities conducted exclusively for the purposes set out **the first subparagraph** ~~in point (a)~~, may cover**, where relevant,** the submission of the application for a marketing authorisation and the offer, manufacture, sale, supply, storage, import, use and purchase of ~~patented~~ 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.

3. This exception **provided for in this Article** shall not cover the placing on the market of the medicinal products resulting from such activities.

~~**1a. Patent rights, or supplementary protection certificates under the [Regulation (EC) No 469/2009 – OP please replace reference by new instrument when adopted] shall not be regarded as infringed by procurement bids and decisions on applications referred to in paragraph 1 point (a).**~~

~~**1b. The procedures and decisions in Paragraph (1) and (1a) shall be considered by Member States as regulatory or administrative procedures which, as such, are independent from the enforcement of intellectual property rights.**~~

~~1c. The protection of intellectual property rights shall not be a valid ground to refuse, suspend, delay, withdraw or revoke decisions related to the procedures referred to in paragraph (1) and (1a). This paragraph is without prejudice to national rules concerning pricing and reimbursement procedures that make the availability of a medicinal product on the market of that Member State conditional to submit an application of pricing and reimbursement., when those rules concern the applicant's activities that can be indirectly affected by intellectual property rights.~~

Article 86

Rewards for paediatric medicinal products

1. Where an application for marketing authorisation, 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, paragraphs 1 and 2 of [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted].

   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 49(2) of this Directive or in Article 90(2) of [revised Regulation (EC) No 726/2004] 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 product is authorised in all Member States.

4. In the case of an application for new **paediatric** therapeutic indications, ~~including paediatric indications, new pharmaceutical forms, new strengths and new routes of administration of authorised medicinal products~~ **for a medicinal product** which ~~are~~ **is** protected either by a supplementary protection certificate under [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate which leads to the authorisation of a new paediatric indication, paragraphs 1, 2 and 3 shall not apply if the applicant applies for, and obtains, a one-year extension of the period of ~~marketing~~ ~~**data**~~ **market** protection 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 81(2), first subparagraph, point (d).

REVISED REGULATION

ORPHAN INCENTIVES

Chapter II
GENERAL PROVISIONS AND RULES ON APPLICATIONS
Section 2
Marketing authorisation decisions

Article 29
Regulatory protection periods

Without prejudice to the law on the protection of industrial and commercial property, medicinal products for human use which have been authorised in accordance with this Regulation shall benefit from the periods of regulatory protection set out in Chapter VII of [revised Directive 2001/83/EC].

CHAPTER VI
ORPHAN MEDICINAL PRODUCTS

~~*Article 70*~~

~~*Orphan medicinal products addressing a high unmet medical need*~~

~~1.~~ ~~An orphan medicinal product shall be considered as addressing a high unmet medical need where it fulfils the following requirements:~~

~~(a)~~ ~~there is no~~ **~~satisfactory method of diagnosis, prevention or treatment in standard of care~~** ~~medicinal product authorised in the Union for such condition or where, despite medicinal products being authorised for such condition in the Union, the applicant demonstrates that the orphan medicinal product, in addition to having a significant benefit, will bring exceptional therapeutic advancement;~~

~~(b)~~ ~~the use of the orphan medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population~~**~~. The meaningful reduction in disease morbidity or mortality for the relevant patient population shall be demonstrated, where possible and appropriate, with data from clinical trials that use a relevant and evidence-based comparator in accordance with scientific advice provided by the Agency.~~**

~~2.~~ ~~A medicinal product for which an application has been submitted in accordance with Article 13 of [revised Directive 2001/83/EC] shall not be considered as addressing a high unmet medical need.~~

~~3.~~ ~~Where t~~**~~T~~**~~he Agency~~ **~~shall~~** ~~adopts scientific guidelines for the application of this Article~~**~~. To this end~~**~~, it shall consult the Commission and the authorities or bodies referred to in Article 162.~~

Article 71

Market exclusivity

1. Where an orphan marketing authorisation is granted and without prejudice to intellectual property law, the Union and the Member States shall not grant a marketing authorisation or ~~**extension of indication to**~~ extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product for the duration of market exclusivity set out in paragraph 2.

2. The duration of market exclusivity shall be as follows:
   (a) ~~nine~~ **ten** years for orphan medicinal products other than those referred to in point~~s (b) and~~ (c);
   ~~(b) ten years for orphan medicinal products addressing a high unmet medical need as referred to in Article 70;~~
   (c) five years for orphan medicinal products which have been authorised in accordance with Article 13 of [revised Directive 2001/83/EC].

3. Where a marketing authorisation holder holds more than one orphan marketing authorisations for the same active substance, those authorisations shall not benefit from separate market exclusivity periods. The duration of the market exclusivity shall start from the date when the first orphan marketing authorisation was granted in the Union.

4. By way of derogation from paragraph 1, and without prejudice to intellectual property law, the marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:
   (a) the marketing authorisation holder for the original orphan medicinal product has given consent to the second applicant, or
   (b) the marketing authorisation holder for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or
   (c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

5. The submission, validation and assessment of the application for the marketing authorisation and granting the marketing authorisation for a generic or biosimilar product to the reference medicinal product for which market exclusivity has expired, shall not be prevented by the market exclusivity of a similar product to the reference medicinal product.

6. The market exclusivity of the orphan medicinal product shall not prevent the submission, validation and assessment of an application for **or granting** a marketing authorisation ~~**for, a medicinal product** **or granting a marketing authorisation,**~~ **including to extend an existing marketing authorisation for a new therapeutic indication**~~**or an extension of an existing marketing authorisation** for~~**of** a similar medicinal product, including generics and biosimilars, where the remainder of the duration of the market exclusivity is less than two years.

7. Where the Agency adopts scientific guidelines for the application of paragraphs 1 and 4, it shall consult the Commission.

Article 72

Prolongation of market exclusivity

~~1. The periods of market exclusivity referred to in Article 71, paragraph 2, points (a) and (b), shall be prolonged by 12 months, where the orphan marketing authorisation holder can demonstrate that the conditions referred to in Article 81(2), point (a), and Article 82(1**a**) [of revised Directive 2001/83/EC] are fulfilled.~~

~~The procedures set out in Articles 82(2) to (5) [of revised Directive 2001/83/EC] shall accordingly apply to the prolongation of market exclusivity.~~

2. The period of market exclusivity shall be prolonged by an additional 12 months for orphan medicinal products referred to in Article 71(2), points (a) ~~and (b)~~, if at least two years before the end of the exclusivity period, the orphan marketing authorisation holder obtains a marketing authorisation for one or more new therapeutic indications for a different orphan condition ~~**where such data were not available when the initial marketing authorisation was submitted**~~.

   Such a prolongation may be granted twice, if the new therapeutic indications are each time for different orphan conditions.

3. The orphan medicinal products which benefit from the prolongation of market exclusivity referred to in the paragraph 2 shall not benefit from the additional period of ~~data~~ **market** protection referred to in Article 8**0** ~~1~~(2) ~~, point (d),~~ of [revised Directive 2001/83/EC].

4. Article 71(3) equally applies to the prolongations of market exclusivity referred to in paragraph~~s 1 and~~ 2.

REPURPOSING BY ANOTHER ACTOR ('CHAMPION')

CHAPTER IV
POST-MARKETING AUTHORISATION MEASURES

Article 48

*Scientific opinion on data submitted from ~~not-for-profit~~ entities **not engaged in an economic activity** for repurposing of authorised medicinal products*

1. An entity not engaged in an economic activity ~~('not-for-profit entity')~~ may submit to the Agency or to a competent authority of the Member State substantive non-clinical or clinical evidence for a new therapeutic indication ~~that is expected to fulfil an unmet medical need~~.

The Agency may, at the request of a Member State, the Commission, or on its own initiative and on the basis of all available evidence make a scientific evaluation of the benefit-risk of the use of a medicinal product with a new therapeutic indication ~~that concerns an unmet medical need.~~ **The Agency shall draw up guidance on the consultation process.**

The opinion of the Agency shall be made publicly available and the competent authorities of the Member States shall be informed.

2. In cases where the opinion is favourable~~,~~ **and the new therapeutic indication addresses an unmet medical need, ~~on the request of the Agency the Agency shall inform Member States and the Commission and request~~** the marketing authorisation holders of the medicinal products concerned **~~to~~** shall submit a variation to update the product information with the new therapeutic indication **~~in accordance with Article 47~~**.

3. Article 8**0**~~1~~(2), **2nd subparagraph** ~~point (de)~~ **and Article 84(1)** of [revised Directive 2001/83/EC] shall not apply for variations under this Article.

Article 4 (Directive)

Definitions

(52) 'entity not engaged in an economic activity' means any legal or natural person that ~~is not engaged in an economic activity and that~~:

(a) is not **profit making** ~~an undertaking or controlled by an undertaking;~~ and,

(b) **is not owned or controlled directly or indirectly by any undertaking or** has not concluded any agreements with any undertaking concerning sponsorship or participation to the medicinal product development;

CHAPTER V
PRE-AUTHORISATION REGULATORY SUPPORT

Article 58

Scientific advice

1. Undertakings or, as relevant, **entities not engaged in an economic activity** ~~not-for-profit entities~~ may request scientific advice as referred to in Article 138(1), second subparagraph, point (p) , from the Agency.

   Such advice can also be requested for medicinal products referred to in Articles 83 and 84 of [revised Directive 2001/83/EC].

2. In the preparation of the scientific advice referred to in paragraph 1 and upon request by undertakings or, as relevant, ~~not-for-profit~~ entities **not engaged in an economic activity** that requested the scientific advice, the Agency may consult experts of the Member States with clinical trial or medical device expertise or the expert panels designated in accordance with Article 106(1) of Regulation (EU) 2017/745.

3. In the preparation of the scientific advice referred to in paragraph 1 and in duly justified cases, the Agency may consult authorities established in other Union legal acts as relevant for the provision of the scientific advice in question or other public bodies established in the Union, as applicable.

4. The Agency shall include in the European public assessment report the key areas of the scientific advice once the corresponding marketing authorisation decision has been taken in relation to the medicinal product, after deletion of any information of a commercially confidential nature.

Article 59

Parallel scientific advice

1. Undertakings or, as relevant, ~~not-for-profit~~ entities **not engaged in an economic activity** established in the Union may request that the scientific advice referred to in Article 58(1) takes place in parallel to the joint scientific consultation carried out by the Member State Coordination Group on Health Technology Assessment, in line with Article 16(5) of Regulation (EU) 2021/2282.

2. In case of medicinal products involving a medical device, undertakings or, as relevant, ~~not-for-profit~~ entities **not engaged in an economic activity** may request scientific advice as referred to in Article 58(1) in parallel with the consultation of the expert panels referred to in Article 61(2) of Regulation (EU) 2017/745 **and Article 48 (6) of Regulation (EU) 2017/746**.

3. In the case of paragraph 2, the scientific advice, as referred to in Article 58(1), shall involve exchanges of information between the respective authorities or bodies and, where applicable, have synchronised timing, while preserving the separation of their respective remits.

Article 60

Enhanced scientific and regulatory support for priority medicinal products ('PRIME')

1. The Agency may offer enhanced scientific and regulatory support, including as applicable consultation with other bodies as referred to in Articles 58 and 59 and accelerated assessment mechanisms, for certain medicinal products that, based on preliminary evidence submitted by the developer fulfil **at least one of** the following conditions:
   (a) are likely to address an unmet medical need as referred to in Article 83(1) of [revised Directive 2001/83/EC];
   (b) ~~are orphan medicinal products~~ ~~**and**~~ **are likely to bring exceptional therapeutic advancement** ~~and are likely to address a high unmet medical need as referred to in Article 70(1)~~;

(c) are expected to be of major interest from the point of view of public health, in particular as regards therapeutic innovation, taking into account the early stage of development, or antimicrobials with any of the characteristics mentioned in Article 40(3)**;**~~.~~

(d) are likely to adress a neglected tropical disease (NTD).

2. The Agency, at the request of the Commission and after consulting the EMA Emergency Task Force, may offer enhanced scientific and regulatory support to developers of a medicinal product preventing, diagnosing or treating a disease resulting from serious cross border threats to health if access to such products is considered necessary to ensure high level of Union preparedness and response to health threats.

3. The Agency may stop the enhanced support if it is established that the medicinal product will not address the identified unmet medical need **or does not have the potential to enhance preparedness and response to serious cross border health threats** to the anticipated extent.

4. The compliance of a medicinal product with the criteria set out in Article 83 of [revised Directive 2001/83/EC] shall be assessed on the basis of the relevant criteria, independently of whether it has received priority medicinal product support under this Article.

CHAPTER IX
REGULATORY SANDBOX

Article 113

Regulatory sandbox

1. The Commission may set up a regulatory sandbox pursuant to a specific sandbox plan, ~~based~~ **taking into account**~~on~~ a recommendation of the Agency and pursuant to the procedure set out in paragraphs 4 to 7, where all **of** the following conditions are met:
   (a) it is not possible to develop the medicinal product or category of **medicinal** products in compliance with the requirements applicable to medicinal products due to scientific or regulatory challenges arising from characteristics or methods related to the product;
   (b) the characteristics or methods referred to in point (a) **likely to** positively and distinctively contribute to the quality, safety or efficacy of the medicinal product or category of products or provide a major ~~advantage~~ contribution to patient access to treatment.

2. The regulatory sandbox shall set out a regulatory framework, including scientific requirements, for the development and, where appropriate**,** clinical trials and placing on the market of a product referred to in paragraph 1 under the conditions set out in this Chapter. The regulatory sandbox may allow targeted derogations to this Regulation, [revised Directive 2001/83/EC]**,** ~~, or~~ Regulation (EC) 1394/2007 ~~**or Regulation (EU) 536/2014**~~ under the conditions set out in Article 114.

   A regulatory sandbox shall take effect under direct supervision of the competent authorities of the Member States concerned with a view to ensuring compliance with the requirements of this Regulation and, where relevant, other Union and Member State legislation concerned by the sandbox. Any violation of the conditions set out in the decision referred to in paragraph 6 and the identification of any risks to health and to environment shall be immediately notified to the Commission and to the Agency.

3. The Agency shall monitor the field of emerging medicinal products and may request information and data from **the national competent authorities of the Member States,** marketing authorisation holders, developers, independent experts and researchers, and representatives of healthcare professionals and of patients and may engage with them in preliminary discussions.

4. Where the Agency considers it appropriate to set up a regulatory sandbox for medicinal products which are likely to fall under the scope of this Regulation, it shall**, following appropriate consultations including consultation with the competent authorities of the Member States,** provide a recommendation to the Commission. The Agency shall list eligible products or category of products in that recommendation and shall include the **recommended** sandbox plan referred to in paragraph 1.

   The Agency shall not recommend to set up a regulatory sandbox for a medicinal product that is already advanced in its development programme.

5. The Agency shall be responsible for developing a sandbox plan based on data submitted by developers of eligible products and following appropriate consultations **including consultation with competent ~~A~~authorities of the Member States**. The **sandbox** plan shall set out clinical, scientific and regulatory justification for a sandbox, including the identification of the requirements of this Regulation, [revised Directive 2001/83/EC]**;** ~~**Regulation (EU) 536/2014**~~ and Regulation (EC) 1394/2007 that cannot be complied with and a proposal for alternative or mitigation measures, where appropriate. The **sandbox** plan shall also include a proposed timeline for the duration of the sandbox. Where appropriate, the Agency shall also propose measures in order to mitigate any possible distortion of market conditions as a consequence of establishing a regulatory **sandbox**.

6. The Commission shall, by means of implementing acts, take a decision on the set up of a regulatory sandbox taking into account the recommendation of the Agency and the sandbox plan pursuant to paragraph 4. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

7. Decisions establishing a regulatory sandbox under paragraph 5 shall be limited in time and shall set out detailed conditions for its implementation. These Decisions shall:
   (a) include ~~the~~ **a** proposed sandbox plan, **taking into account the recommended sandbox plan of the Agency**;
   (b) include the duration of the regulatory sandbox and its expiry;
   (c) include as part of the sandbox plan the requirements of this Regulation and of [revised Directive 2001/83/EC]**, Regulation (EC) 1394/2007 ~~or Regulation (EU) 536/2014~~** that cannot be complied with and shall include appropriate measures to mitigate potential risks to health and to the environment.

8. The Commission may, by means of implementing acts, suspend or revoke a regulatory sandbox at any time. in any of the following cases:
   (a) the requirements and conditions laid down in paragraphs 6 and 7 are no longer met;
   (b) it is appropriate to protect public health.

   Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

   Where the Agency receives information that one of the cases referred to in the first subparagraph may be fulfilled, it shall inform the Commission accordingly.

9. Where after the ~~D~~**d**ecision to establish the regulatory sandbox in accordance with paragraph 6, risks to health are identified but these risks can be fully mitigated by the adoption of supplementary conditions, the Commission may, after consultation of the Agency, amend its decision **referred to paragraphs 7 or to restart the sandbox following a suspension under paragraph 8** by means of implementing acts. The Commission may also prolong the duration of a regulatory sandbox by means of implementing acts. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

10. This Article shall not ~~exclude the setting up of~~ **apply to** time limited pilot projects to test different ways of implementing the applicable legislation.

Article 114

Products developed under a sandbox

1. When authorising a clinical trial application for products covered by a regulatory sandbox, Member States shall take the sandbox plan referred to in Article 113(1) into consideration.

2. A medicinal product developed as part of a regulatory sandbox ~~may~~ **shall** be placed on the market only when authorised in accordance with ~~**Article 5 of**~~ this Regulation. The initial validity of such authorisation shall not exceed the duration of the regulatory sandbox. The authorisation may be prolonged at the request of the marketing authorisation holder.

3. In duly justified cases, the marketing authorisation of a medicinal product developed under the regulatory sandbox may include derogations from the requirements set out in this Regulation and [revised Directive 2001/83/EC]**, Regulation (EC) 1394/2007** ~~**or Regulation (EU) 536/2014**~~. Those derogations may entail adapted, enhanced, waived or deferred requirements. Each derogation shall be limited to what is apt and strictly necessary to attain the objectives pursued, duly justified and specified in the conditions to the marketing authorisation.

   ~~**These derogations shall not cover the ethical assessment organised pursuant to Article 8, paragraph 4 of Regulation (EU) 536/2014.**~~

4. For medicinal products developed as part of a regulatory sandbox for which a marketing authorisation has been granted in accordance with paragraph 2 and where appropriate paragraph 3, the summary of product characteristics and the package leaflet shall indicate that the medicinal product has been developed as part of a regulatory sandbox. **This condition applies for the duration of the regulatory sandbox.**

5. Without prejudice to Article 195 of [revised Directive 2001/83/EC], the Commission shall suspend **or revoke** a marketing authorisation granted in accordance with paragraph 2, where the regulatory sandbox has been suspended or revoked in accordance with Article 113(7).

6. The Commission shall immediately vary the marketing authorisation to take account of the mitigation measures taken in accordance with Article 115.

Article 115

General sandbox provisions

1. The regulatory sandboxes shall not affect the supervisory and corrective powers of the competent authorities. In case of identification of risks to public health or safety concerns associated with the use of products covered by a sandbox, competent authorities shall take immediate and adequate temporary measures in order to suspend or restrict their use and inform the Commission in accordance with Article 113(2).

   Where such mitigation is not possible or proves to be ineffective, the development and testing process shall be suspended without delay until an effective mitigation takes place.

2. Participants in ~~T~~the regulatory sandbox~~, in particular the marketing authorisation holder of the medicinal product concerned,~~ shall remain **~~is without prejudice to rules related to~~** liable **~~liability~~** under applicable Union and Member States liability legislation for any harm inflicted on third parties as a result from the testing taking place in the sandbox. **~~2a.~~**They **~~Entities implementing the sandbox~~** shall inform the Agency without undue delay of any information which might entail the amendment of the regulatory sandbox or concerns the quality, safety or efficacy of products developed as part of a regulatory sandbox.

3. The modalities and the conditions of the operation of the regulatory sandboxes, including the eligibility criteria and the procedure for the application, selection, participation and exiting from the sandbox, and the rights and obligations of the participants shall be set out in implementing acts. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

4. The Agency with input from Member States shall submit annual reports to the Commission on the results from the implementation of a regulatory sandbox, including good practices, lessons learnt and recommendations on their setup and, where relevant, on the application of this Regulation and other Union legal acts supervised within the sandbox. These reports shall be made publicly available by the Commission.

5. The Commission shall review the reports and put forward, as appropriate, legislative proposals with a view to update the regulatory framework referred to in Article 113(2) or delegated acts in accordance with Article 28 of [revised Directive 2001/83/EC].

CHAPTER III
INCENTIVES FOR THE DEVELOPMENT OF 'PRIORITY ANTIMICROBIALS'

Article 40

Granting the right to a transferable data exclusivity voucher

1. Following a request by the applicant when applying for a marketing authorisation, the Commission may, by means of implementing acts, grant a transferable data exclusivity voucher to a 'priority antimicrobial' referred to in paragraph 3, under the conditions referred to in paragraph 4 based on a scientific assessment by the Agency.

2. The voucher referred to in paragraph 1 shall give the right to its holder to an additional 12 months of data protection **within the meaning of Article 80 paragraph 1 of [revised Directive 2001/83/EC]** for one authorised medicinal product.

3. An antimicrobial shall be considered 'priority antimicrobial' if **it addresses a multi-drug resistant organism and serious or a life-threatening infection, the** preclinical and clinical data underpin a significant clinical benefit with respect to antimicrobial resistance and it has at least one of the following characteristics:
   (a) it represents a new class of antimicrobials;
   (b) its mechanism of action is distinctly different from that of any authorised antimicrobial in the Union;
   (c) it contains an active substance not previously authorised in a medicinal product in the Union ~~that addresses a multi-drug resistant organism and serious or life-threatening infection~~.

   In the scientific assessment of the criteria referred to in the first subparagraph, and in the case of antibiotics, the Agency shall take into account the 'WHO priority pathogens list for R&D of new antibiotics', or an equivalent list established at Union level.

4. To be granted the voucher by the Commission, the applicant shall:
   (a) demonstrate capacity to supply the priority antimicrobial in sufficient quantities for the expected needs of the Union market;
   (b) provide information on all direct financial support received for research related to the development of the priority antimicrobial.
   (c) demonstrate that the application for granting a marketing authorisation of the priority antimicrobial has been first submitted to the Agency or has been submitted no later than 90 days after the submission of the application for the first marketing authorisation outside the European Union.

   Within 30 days after the marketing authorisation is granted, the marketing authorisation holder shall make the information referred to in point (b) accessible to the public via a dedicated webpage and shall communicate, in a timely manner the electronic link to that webpage to the Agency.

5. Once the marketing authorisation is granted, the Agency shall inform without undue delay the MSSG, in accordance with Article ~~130~~ 131 paragraph 2~~, second subparagraph, to initiate the procedure~~ with a view to propose a ~~for~~ the potential inclusion of the priority antimicrobial on the Union list of critical medicinal products~~, in agreement with the procedure set out in Article 131 of the Regulation~~.

~~**5. When adopting the implementing act referred to in paragraph 1, the estimated cost of the voucher, including the actual and expected costs of already used vouchers, and the risk of overcompensation based on the data provided in accordance with paragraph 4(b) shall be considered in addition to the conditions in paragraph 1. In case the estimated cost of the voucher, including the actual and expected costs of already used vouchers, and the risk of overcompensation, overrides the clinical benefit with respect to antimicrobial resistance, the voucher shall not be granted.**~~

Article 170

Evaluation

(…)

6. The Commission shall, following the use of the first two vouchers pursuant to Article 41, paragraph 2, or five years after the date of application of this Regulation, whichever is the earliest, and every 5 years thereafter ~~pursuant to Article 41, paragraph 2,~~ carry out an evaluation of Chapter III of this Regulation and present a report on the main findings of that evaluation to the European Parliament and the Council. The evaluation shall include an assessment of the effectiveness of the voucher as a measures, taking into account also other existing Union level market incentives for authorised priority antimicriobials, to address the market failure in the development of new antimicrobials addressing antimicrobial resistance and assess the actual and expected costs. The Commission shall, if appropriate, present a legislative proposal, based on the evaluation, in order to amend this Regulation.

Article 41

Transfer and use of the voucher

1. A voucher may be used to **add** ~~extend the data protection for a period of~~ 12 months **of data protection within the meaning of Article 80 paragraph 1 of [revised Directive 2001/83/EC],** of the priority antimicrobial or another medicinal product authorised in accordance with this Regulation of the same or different marketing authorisation holder.

A voucher can be transferred at any time before its use. A voucher **may** ~~shall only~~ be used once **only** and in relation to a single centrally authorised medicinal product**.** ~~and only if that product is within its first **six** four years of regulatory data protection.~~
In case of a medicinal product other than the priority antimicrobial concerned~~, while the the voucher can be transferred any time before the use~~, the use of the voucher can take place only in the fifth ~~sixth~~ year of the regulatory data protection period and if the marketing authorisation holder demonstrates that the ~~and its average~~ annual gross sales of ~~the~~ that medicinal product~~s~~ in the Union during any of the ~~Y years~~ preceding four years ~~the use of the voucher does not~~ have not exceeded ~~X~~ 490 million euros.

~~A voucher may only be used if the marketing authorisation of the priority antimicrobial for which the right was initially granted has not been withdrawn.~~

1a. The marketing authorisation holder shall demonstrate that information about the annual gross sales referred to in para (1) is accurate and complete and that it has been audited by an independent external auditor.

~~**The additional data protection period shall not apply if the annual gross sales of the medicinal product concerned in the Union exceeds the amount referred to in point 1 of this Article.**~~

~~**The Commission is empowered to adopt delegated acts in accordance with Article 175 of this Regulation to adjust this amount with the rate of the inflation.**~~

A voucher may only be used if the marketing authorisation of the priority antimicrobial for which the right was initially granted has not been withdrawn.

2. To use the voucher, its owner shall apply for a variation of the marketing authorisation concerned in accordance with Article 47 to extend the data protection.

3. A voucher may be transferred to another marketing authorisation holder and shall not be transferred further.

4. A marketing authorisation holder to whom a voucher is transferred shall notify the Agency of the transfer within 30 days, stating the value of the transaction between the two parties. The Agency shall make this information publicly available **on its webpage**.

Article 42

Validity of the voucher

1. A voucher shall cease to be valid in the following cases:
   (a) where the Commission adopts a decision in accordance with Article 47 to extend the data protection of the receiving medicinal product;
   (b) where it is not used within 5 years from the date it was granted.

2. The Commission may revoke the voucher prior to its transfer as referred to in Article 41(3) if a request for supply **by any Member State or the Commission**, procurement or purchase of the priority antimicrobial in the Union has not been fulfilled.

3. Without prejudice to patent rights, or supplementary protection certificates[48], if a priority antimicrobial is withdrawn from the Union market prior to expiry of the periods of market and data protection laid down in Articles 80 and 81 of [revised Directive 2001/83/EC], those periods shall not prevent the validation, authorisation and placing on the market of a medicinal product using the priority antimicrobial as a reference medicinal product in accordance with Chapter II, Section 2 of [revised Directive 2001/83].

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48 Regulation (EC) No 469/2009 of the European Parliament and of the Council, (OJ L 152, 16.6.2009, p. 1).

Article 43

Duration of application of Chapter III

This Chapter shall apply**, ~~subject~~ taking ~~to~~ into account ~~of~~ the outcome of the evaluations referred to in Article 170 paragraph 6,** until [*Note to OP: insert the date of 15 years after the date of entry into force of this Regulation*] or until the date when the Commission has granted a total of 10 vouchers in accordance with this Chapter, whichever date is the earliest.

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Article 4

Definitions

(22) '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**,** ~~and~~antifungals **and antiprotozoals**;

3RD READING PACKAGE:

ORPHAN AND PAEDIATRICS

Recitals

REVISED DIRECTIVE

(25) In order to ensure that the data supporting the marketing authorisation concerning the use of a product in children to be authorised under this regulation have been correctly developed, the competent authorities should check compliance with the agreed paediatric investigation plan and any waivers and deferrals at the validation step for marketing authorisation applications.

(77) 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 then 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 Agency should be informed in good time of any such intention and should make that intention publicly available.

(142) 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 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. In order to ensure that the data supporting the marketing authorisation concerning the use of a product in children, the competent authorities responsible for the authorisation of a medicinal product should check compliance with the agreed paediatric investigation plan and any waivers and deferrals at the validation step for marketing authorisation applications.

(143) 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, independently from the fact that they support or not the use of the medicinal product in children, appropriate information should be included in the summary of product characteristics and, if appropriate, in the package leaflet. Information on waivers should also be included in product information. When all the measures 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.

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(86) Medicinal products for rare diseases and for children should be subject to the same provisions as any other medicinal product concerning their quality, safety and efficacy, for example for what concerns the marketing authorisation procedures, the pharmacovigilance and quality requirements. However, specific requirements also apply to them. Such requirements, which are currently defined in separate legislations, should be integrated in this Regulation in order to ensure clarity and coherency of all the measures applicable to these medicinal products.

(87) Some orphan conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition cannot be recovered by the expected sales of the medicinal product. However, patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is therefore necessary to stimulate the research, development and placing on the market of appropriate medications by the pharmaceutical industry.

(88) Regulation (EC) No 141/2000 of the European Parliament and of the Council[49] has proved to be successful in boosting developments of orphan medicinal products in the Union; therefore an action at Union level remains preferable to uncoordinated measures by the Member States which may result in distortions of competition and barriers to intra-Union trade.

[49] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p. 1).

(89) The open and transparent Union procedure for the designation of potential medicinal products as orphan medicinal products established by Regulation (EC) No 141/2000 should be maintained. To increase legal clarity and simplification, the specific legal provisions applicable to these medicinal products should be integrated in this Regulation.

(90) Objective criteria for the orphan designation based on the prevalence of the life-threatening or chronically debilitating condition for which diagnosis, prevention or treatment is sought and the existence of no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Union should be maintained; a prevalence of not more than five affected persons per 10 000 is generally regarded as the appropriate threshold. ~~The orphan designation criterion on the basis of return on investment has been abolished, since it has never been used.~~

(91) The criterion for orphan designation based on prevalence of a disease may, however, not be appropriate to identify rare diseases in all cases. For example, for conditions which have a short duration and high mortality, measuring the number of people that acquired the disease during a specific time period would better reflect if it is rare within the meaning of this Regulation than measuring the number of people who are 'affected by it' in a specific moment of time. With the aim to better identify only those diseases which are rare, the Commission should be empowered to set up specific designation criteria for certain conditions if the one provided for are not appropriate due to scientific reasons and on the basis of a recommendation of the Agency.

(92) With the aim to better identify only those diseases which are rare, the Commission should be empowered to supplement the designation criteria by a delegated act if they are not appropriate for certain conditions due to scientific reasons and on the recommendation of the Agency. In addition, the designation criteria require implementing measures to be adopted by the Commission.

(93) If a satisfactory method of diagnosis, prevention or treatment of the condition in question has already been authorised in the Union, the orphan medicinal product will have to be of significant benefit to those affected by that condition. In this context, a medicinal product authorised in one Member State is generally deemed as being authorised in the Union. It is not necessary for it to have Union authorisation or to be authorised in all Member States to be considered as a satisfactory method. In addition, commonly used methods of diagnosis, prevention or treatment that are not subject to a marketing authorisation may be considered satisfactory if there is scientific evidence of their efficacy and safety. In certain cases, medicinal products prepared for an individual patient in a pharmacy according to a medical prescription, or according to the prescriptions of a pharmacopoeia and intended to be supplied directly to patients served by the pharmacy, may be considered as satisfactory treatment if they are well known and safe and this is a general practice for the relevant patient population in the Union.

(94) The competence to designate a medicinal product as an orphan medicinal product, in the form of a decision, is accorded to the Agency. This is expected to facilitate and expedite the designation procedure, while ensuring high level of scientific expertise.

(95) In order to incite faster authorisation of designated orphan medicinal products, the validity of orphan designation has been set at seven years, with the possibility of extension by the Agency under certain specified conditions; the orphan designation may be withdrawn at the request of the orphan medicine sponsor.

(96) The Agency is responsible for designation of an orphan medicinal product as well as for the setting up and management of a register of designated orphan medicinal products. That register should be publicly available and the minimum data which should be included in the register have been specified in this Regulation with the empowerment for the Commission to amend or supplement this data by a delegated act.

(97) Sponsors of orphan medicinal products designated under this Regulation should be entitled to the full benefit of incentives granted by the Union or by the Member States to support the research and development of medicinal products for the diagnosis, prevention or treatment of such conditions, including rare diseases.

(98) Patients suffering from orphan conditions deserve medicinal products of the same quality, safety and efficacy as other patients; orphan medicinal products should therefore be submitted to the normal evaluation process carried out by the Committee of Medicinal Products for Human Use for the applicant to obtain an marketing authorisation for orphan medicinal product, while a separate marketing authorisation may be granted for indications not fulfilling the criteria of an orphan medicinal product.

(106) Before a medicinal product for human use is placed on the market in one or more Member States, it has to have undergone extensive studies, including non-clinical tests and clinical trials, to ensure that it is safe, of high quality and effective for use in the target population. It is important that such studies are undertaken also on the paediatric population in order to ensure that medicinal products are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric population. It is also important that medicinal products are presented in dosages and formulations adequate for the use in children.

(107) Therefore, the development of medicinal products that could potentially be used for the paediatric population should become an integral part of the development of medicinal products, integrated into the development programme for adults. Thus, paediatric investigation plans should be submitted early during medicinal product development, in time for studies to be conducted in the paediatric population, where appropriate, before marketing authorisation applications are submitted.

(108) As the development of medicinal products is a dynamic process dependent on the result of ongoing studies, in certain cases, for example when limited information on the medicinal products are available because the medicinal products are tested for the first time in the paediatric population, a specific procedure allowing to progressively build up a paediatric investigation plan should be put in place.

(109) During public health emergencies, in order not to delay a prompt authorisation of a medicinal product intended for the treatment or the prevention of a condition related to the public health emergency, there should be a possibility to temporarily waive the requirements concerning paediatric studies to be submitted at the moment of marketing authorisation.

(110) In order to not endanger the health of children and avoid to expose them to unnecessary clinical trials, the obligation to agree and conduct paediatric studies in children should be waived when the medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population, the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for children or the disease for which the medicinal product is intended occurs only in adult populations. Nevertheless, in the last case, if on the basis of existing scientific evidence, the medicinal product due to its molecular mechanism of action is expected to be effective against a different disease in children, the obligation should be maintained.

(111) To ensure that research in the paediatric population is only conducted to meet their therapeutic needs, the Agency should agree and make public lists of waivers for medicinal products and for specific medicinal products or for classes or part of classes of medicinal products. As knowledge of science and medicine evolves over time, provision should be made for the lists of waivers to be amended. However, if a waiver is revoked, that requirement should not apply for a given period in order to allow time for at least a paediatric investigation plan to be agreed and studies in the paediatric population to be initiated before an application for marketing authorisation is submitted.

(112) With a view to ensuring that research is conducted only when safe and ethical and that the requirement for study data in the paediatric population does not block or delay the authorisation of medicinal products for other populations, the Agency may defer the initiation or completion of some or all of the measures contained in a paediatric investigation plan for a limited period of time. Such deferral should be extended only in duly justified cases.

(113) The possibility to modify an agreed paediatric investigation plan should be foreseen when the applicant encounters such difficulties with its implementation as to render the plan unworkable or no longer appropriate.

(114) The Agency, after consultation of the Commission and of interested parties, should draw up the details of the content of an application for agreement of a paediatric investigation plan, for its modification, for waivers and for deferral requests.

(115) For medicinal products intended to be developed for use only in children which would be developed independently from the current provisions, simplified details of the paediatric investigation plan should be required.

(116) To ensure that the data supporting the marketing authorisation concerning the use of a medicinal product in children to be authorised under this Regulation have been correctly developed, the Committee for Medicinal Products for Human Use should check compliance with the agreed paediatric investigation plan and any waivers and deferrals at the validation step for marketing authorisation applications.

(117) Free scientific advice should be provided by the Agency as an incentive to sponsors developing medicinal products for the paediatric population.

(118) 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, independently from the fact that they support or not the use of the medicinal product in children, should be included in the summary of product characteristics and, if appropriate, in the package leaflet.

(119) To sustain the development of novel, paediatric only indications from authorised medicinal products no longer covered by intellectual property rights, it is necessary to establish a specific type of marketing authorisation, the Paediatric Use Marketing Authorisation. A Paediatric Use Marketing Authorisation should be granted through existing marketing authorisation procedures but should apply specifically for medicinal products developed exclusively for use in the paediatric population. It should be possible for the name of the medicinal product that has been granted a Paediatric Use Marketing Authorisation to retain the existing brand name of the corresponding medicinal product authorised for adults, in order to capitalise on existing brand recognition, while benefiting from the regulatory protection associated with a new marketing authorisation.

(120) An application for a Paediatric Use Marketing Authorisation should include the submission of data concerning use of the medicinal product in the paediatric population, collected in accordance with an agreed paediatric investigation plan. These data may be derived from the published literature or from new studies. An application for a Paediatric Use Marketing Authorisation should also be able to refer to data contained in the dossier of a medicinal product which is or has been authorised in the Union. This is intended to provide an additional incentive to encourage SMEs, including generic companies, to develop off-patent medicinal products for the paediatric population.

(121) Some paediatric investigation plans may be discontinued due to various reasons despite possible positive results for the treatment of children obtained from the studies already conducted. The information of such discontinuations and their reasons should be collected by the Agency and made public in order to inform eventual third parties who may be interested in continuing the above-mentioned studies.

(122) To increase the transparency on clinical trials conducted in children in third countries and referred to in a paediatric investigation plan or conducted from a marketing authorisation holder independently from a paediatric investigation plan, information on these clinical trials should be included in the European clinical trial database created by Regulation (EU) No 536/2014.

(123) The summary of the results of all the paediatric clinical trials included in the European clinical trial database created by Regulation (EU) No 536/2014 should be made publicly available within 6 months after the end of the clinical trials unless this is not possible for justified scientific reasons.

(124) To discuss priority in medicinal product development, in particular in areas of unmet medical need for children and to coordinate studies relating to paediatric medicinal products, the Agency should set up a European network composed of patient representatives, academics, medicines developers, investigators and research centres based in the Union or in the European Economic Area.

(125) Union funding should be provided to cover all aspects of the work of the Agency resulting from paediatric related activities, such as the assessment of paediatric investigation plans, fee waivers for scientific advice, and information and transparency measures, including the database of paediatric studies and the network.

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CHAPTER VI
ORPHAN MEDICINAL PRODUCTS

Article 63

Criteria for orphan designation

1. A medicinal product that is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition shall be designated as an orphan medicinal product where the orphan medicine sponsor can demonstrate that the following requirements are met:
   (a) the condition affects not more than five in 10 000 persons in the Union when the application for an orphan designation is submitted **and**;
   (b) there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Union or, where such method exists, that the medicinal product would be of significant benefit to those affected by that condition.

2. By way of derogation from paragraph 1, point (a), and on the basis of a recommendation from the Agency, when the requirements specified in paragraph 1, point (a), are not appropriate due to the specific characteristics of certain conditions or any other scientific reasons, the Commission is empowered to adopt delegated acts in accordance with Article 175 in order to supplement paragraph 1, point (a), by setting specific criteria for certain conditions.

3. The Commission shall adopt the necessary provisions for implementing this Article by means of implementing acts in accordance with the procedure laid down in Article 173(2) in order to further specify the requirements referred to in paragraph 1.

Article 64

Granting an orphan designation

1. The orphan medicin**al producte** sponsor shall submit an application for the designation of the orphan medicinal product to the Agency at any stage of the development of the medicinal product before the application for marketing authorisation referred to in Articles 5 and 6 is submitted.

2. The application of the orphan medicine sponsor shall be accompanied by the following particulars and documentation:
   (a) name or corporate name and permanent address of the orphan medicine sponsor;
   (b) active substances of the medicinal product;
   (c) proposed condition for which it is intended or the proposed therapeutic indication;
   (d) justification that the criteria laid down in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2) are fulfilled and a description of the stage of development, including the expected therapeutic indication.

   The orphan medicine sponsor shall be responsible for the accuracy of the particulars and documentation.

3. The Agency shall, in consultation with the Member States, the Commission and interested parties, draw up detailed guidelines on the required procedure, format and content of applications for designation and for the transfer of the orphan designation pursuant to Article 65.

4. The Agency shall adopt a decision granting or refusing the orphan designation based on the criteria referred to in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2) within 90 days of the receipt of a valid application. **The Agency shall verify the validity of the application and prepare a summary report. Whenever appropriate, the Agency may ask the applicant to submit additional particulars and documents, in which case the time-limit of 90 days shall be suspended until the supplementary information requested has been provided.** The application is considered valid if it includes all the particulars and documentation referred to in paragraph 2.

   For the purpose of establishing whether the orphan designation criteria are fulfilled, the Agency **shall** ~~may~~ consult the Committee for Medicinal Products for Human Use**. The Committee for Medicinal Products for Human Use shall ensure,as necessary, the appropriate involvement of the relevant scientific expertise through at least** ~~or~~ one of **the** ~~its~~ working parties referred to in Article 150(2), first subparagraph. The outcome of such consultations**, including information on the involvement of relevant scientific expertise,** shall be annexed to the decision, as part of the scientific conclusions of the Agency which justify the decision. **In case of matters not requiring complex scientific assessment, the Agency may take decisions without the consultation referred to in this subparagraph.**

   The decision together with the Annexes referred to in this paragraph shall be notified to the applicant.

5. Decisions of the Agency on granting or refusing the orphan designation shall be made public after deletion of any information of a commercially confidential nature.

Article 65

Transfer of orphan designation

1. The orphan designation may be transferred from a current orphan medicine sponsor to a new orphan medicine sponsor. The transfer shall be subject to prior approval by the Agency, following the submission of an application for the transfer to the Agency.

2. The application of the current orphan medicine sponsor shall be accompanied by the following particulars and documentation:
   (a) name or corporate name and permanent address of the current and new orphan medicine sponsor;
   (b) decision on granting an orphan designation as referred to in Article 64(4);
   (c) designation number as referred to in Article 67(3), point (e).

3 The Agency shall adopt a decision granting or refusing the transfer of the orphan designation within 30 days of the receipt of a valid application by the current orphan medicine sponsor. The application is considered valid if it includes all the particulars and documentation referred to in paragraph 2. The Agency shall address its decision to the current and new orphan medicine sponsor.

Article 66

Validity of orphan designation

1. An orphan designation shall be valid for seven years. During this period, the orphan medicine sponsor shall be eligible for incentives referred to in Article 68.

2. By way of derogation from paragraph 1, on the basis of a justified request of the orphan medicine sponsor, the Agency may extend the validity, where the orphan medicine sponsor can provide evidence that the relevant studies supporting the use of the designated orphan medicinal product in the applied conditions are ongoing and promising with regard to the filing of a future application. **The Agency, shall consult, where necessary, Committee for Medicinal Products for Human Use and the outcome of the consultation shall be annexed to the decision.** Such an extension shall be limited in time, taking into account the expected remaining time needed to file an application for marketing authorisation.

3. By way of derogation from paragraph 1, where an orphan designation is valid at the time when a marketing authorisation for an orphan medicinal product has been submitted in accordance with Article 5, the orphan designation shall remain valid until a decision is adopted by the Commission in accordance with Article 13(2).

4. An orphan designation ceases to be valid once an orphan medicine sponsor has obtained a marketing authorisation for the relevant medicinal product in accordance with Article 13(2).

5. At any time, an orphan designation may be withdrawn at the request of the orphan medicine sponsor.

Article 67

Register of designated orphan medicinal products

1. The register of designated orphan medicinal products shall list all designated orphan medicinal products. It shall be set up and managed by the Agency and be publicly available.

2. Where an orphan designation ceases to be valid or is withdrawn pursuant to Article 66, the Agency shall make an entry in the register of designated orphan medicinal products.

3. The information on the designated orphan medicinal product entered in the register of designated orphan medicinal products shall include at least the following:
   (a) the information on the active substance;
   (b) the name and address of the orphan medicine sponsor;
   (c) the condition for which it is intended or the proposed therapeutic indication;
   (d) the designation date;
   (e) the designation number;
   (f) the decision on granting the orphan designation.

4. The Commission shall be empowered to adopt delegated acts in accordance with Article 175 in order to amend the information to be included in the register of designated orphan medicinal products referred to in paragraph 3 to ensure appropriate information of the users of that register.

Article 68

*Protocol assistance and research support for **designated** orphan medicinal products*

1. The orphan medicine sponsor may, prior to the submission of an application for marketing authorisation, request advice from the Agency on the following:
   (a) the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product, as referred to Article 138(1), second subparagraph, point (p);
   (b) the demonstration of significant benefit within the scope of the designated orphan indication;
   (c) the demonstration of similarity to or clinical superiority over other medicinal products, which have market exclusivity for the same indication.

2. Medicinal products designated as orphan medicinal products under the provisions of this Regulation shall be eligible for incentives made available by the Union and by the Member States to support research into, and the development and availability of, orphan medicinal products and in particular aid for research for small- and medium-sized undertakings **and entities not engaged in economic activities,** provided for in framework programmes for research and technological development.

Article 69

Orphan marketing authorisation

1. Applications for an orphan marketing authorisation shall be submitted in accordance with Articles 5 and 6 and the related marketing authorisation shall be obtained in accordance with Articles 13(2).

2. In addition, the applicant shall demonstrate that the medicinal product has been granted an orphan designation and that the criteria set out in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2) are fulfilled for the therapeutic indication sought.

~~Where appropriate, the applicant shall provide relevant evidence to demonstrate that the medicinal product addresses a high unmet medical need as specified in Article 70(1).~~

3. The Committee for Medicinal Products for Human Use shall assess whether the medicinal product fulfils the requirements set out in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2). **The Committee for Medicinal Products for Human Use shall ensure, as necessary, the appropriate involvement of scientific expertise regarding orphan medicines.** ~~In the situation referred in paragraph 2, subparagraph 2, that Committee shall also assess whether the medicinal product addresses a high unmet medical need as specified in Article 70(1).~~

   Such assessment shall be subject to the same timelines as the application for the marketing authorisation itself and detailed conclusions of such assessment shall be part of the scientific opinion of the Committee for Medicinal Products for Human Use in accordance with Article 12(1).

   The assessment and its conclusions shall be part of the opinion referred to in Article 12(1) and, where relevant, the opinion referred to in Article 12(3).

5. **By way of derogation of article 5(2) of [the revised Directive 2001/83],** ~~T~~the orphan marketing authorisation shall cover only those therapeutic indications, which fulfil the requirements set out in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2) at the time when the orphan marketing authorisation is granted.

6. If after the submission of an application for the orphan marketing authorisation and prior to the opinion of the Committee for Medicinal Products for Human Use the orphan designation is withdrawn in accordance with Article 66(5), the application for the orphan marketing authorisation shall be treated as the application for a marketing authorisation in accordance with Article 6.

7. An applicant may submit an application for a separate marketing authorisation for other indications which do not fulfil the requirements set out in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2).

Article 73

Union financial contribution related to orphan medicinal products

The working arrangements referred to in Article 8 of [new fee Regulation][50] shall set out total or partial reductions for the applicable fees and charges payable to the European Medicines Agency as laid down in [new fee Regulation]. Such reductions shall be covered by the Union contribution provided for in Article 154(3), point (a) of this Regulation.

CHAPTER VII
PAEDIATRIC MEDICINAL PRODUCTS

Article 74

Paediatric investigation plan

1. A paediatric investigation plan shall specify the timing and all the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned. In addition, it shall describe any measures to adapt the pharmaceutical form, the strength, the route of administration and the eventual administration device of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.

2. By derogation from paragraph 1, in the following cases an applicant may submit only an initial paediatric investigation plan as referred to in the second subparagraph:
   (a) when the active substance concerned is not yet authorised in any medicinal product in the EU and is intended to **diagnose, prevent or** treat a ~~novel~~ paediatric condition **via a novel mode of action; or**;
   (b) following the acceptance by the Agency of a justified request from an applicant in accordance with paragraph 3.

[50] Regulation [XXX] of the European Parliament and of the Council on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council [OJ L X, XX.XX.XXXX, p. X].

An initial paediatric investigation plan shall contain only the details and the timing of the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned, that are known at the moment of the submission of the request for agreement mentioned in Article 76(1).

This initial paediatric investigation plan shall also provide a precise timing of when updated versions of the paediatric investigation plan are to be submitted and when a final paediatric investigation plan complying with all the particulars described in paragraph 1, is expected to be submitted to the Agency.

3. When it is not possible, on the basis of scientifically justified reasons, to have a complete paediatric **investigation** ~~development~~ plan in accordance with the timing given in Article 76(1) an applicant may submit a justified request to the Agency to utilise the procedure mentioned in paragraph 2. The Agency has 20 days to accept or refuse the request and shall immediately inform the applicant and state the reasons for refusal.

4. On the basis of the experience acquired as a result of the operation of this Article or of scientific knowledge, the Commission is empowered to adopt delegated acts in accordance with Article 175 to amend the grounds for granting the possibility to utilise the adapted procedure foreseen in paragraph 2.

Article 75

Waivers

1. In accordance with the procedure set out in Article 78, the Agency**, in consultation with Committee for Medicinal Products for Human Use to ensure the necessary involvement of adequate scientific expertise for paediatric medicines,** may decide that the production of the information referred to in, Article 6(5), point (a), of [revised Directive 2001/83], shall be waived for products or for classes of medicinal products, if there is evidence showing any of the following:
   (a) that the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population;

(b) that the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations, **except** ~~unless~~ when the product is directed at a molecular target **or pathway** that on the basis of existing scientific data, is responsible for a different disease or condition in the same therapeutic area in children than the one for which the specific medicinal product or class of medicinal products is intended for in the adult population;

(c) that the specific medicinal product is likely to not represent a significant therapeutic benefit over existing **methods of diagnosis, prevention or** treatments for paediatric patients.

2. The waiver provided for in paragraph 1 may be issued with reference either to one or more specified subsets of the paediatric population, or to one or more specified therapeutic indications, or to a combination of both.

3. On the basis of the experience acquired as a result of the operation of this Article or of scientific knowledge the Commission is empowered to adopt delegated acts in accordance with Article 175 to amend the grounds for granting a waiver detailed in paragraph 1.

Article 76

Validation of a paediatric investigation plan or of a waiver

1. A paediatric investigation plan or an application for waiver shall be submitted to the Agency**, in consultation with Committee for Medicinal Products for Human Use and as necessary the relevant working parties established under Article 150,** with a request for agreement, except in duly justified cases, before the initiation of safety and efficacy clinical studies so as to ensure that a decision on use in the paediatric population of the medicinal product concerned can be given at the time of the marketing authorisation or other application concerned. **The Committee for Medicinal Products for Human Use shall ensure, as necessary, the involvement of scientific expertise regarding paediatric medicinal products. The outcome of this consultation, including details on the involvement of scientific expertise and Member State representation, shall be annexed to the decision.**

2. Within 30 days following receipt of the request referred to in paragraph 1, the Agency shall verify the validity of the request and communicate the result to the applicant.

3. Whenever appropriate, the Agency may ask the applicant to submit additional particulars and documents, in which case the time-limit of 30 days shall be suspended until the supplementary information requested has been provided.

4. In consultation with the Commission**, the national competent authorities** and with interested parties, the Agency shall draw up and publish guidelines for the practical application of this Article.

Article 77

Agreement on a paediatric investigation plan

1. After the validation of the proposed paediatric investigation plan referred to in Article 74(1).which is valid in accordance with the provisions of Article 76(2), the Agency shall adopt within 90 days a decision as to whether or not the proposed studies will ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof, and as to whether or not the expected therapeutic benefits, where appropriate also over existing treatments, justify the studies proposed. When adopting its decision, the Agency shall consider whether or not the measures proposed to adapt the pharmaceutical form, the strength, the route of administration and the eventual administration device of the medicinal product for use in different subsets of the paediatric population are appropriate.

2. After the validation of the proposed initial paediatric investigation plan prepared in accordance with the adapted procedure referred to in Article 74(2) first subparagraph, which is valid in accordance with the provisions of Article 76(2), the Agency shall adopt a decision within 70 days as to whether or not the paediatric investigation plan is expected to ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof, and as to whether or not the expected therapeutic benefits, where appropriate also over existing treatments, justify the studies envisaged.

3. After receiving an updated version of the paediatric investigation plan referred to in Article 74(2), third subparagraph, the Agency shall review it within 30 days.

   After the timeframe laid down in the first subparagraph, without any request from the Agency in accordance with paragraph 5, the updated version of the paediatric investigation plan shall be considered as agreed.

4. When the final paediatric investigation plan referred to in Article 74(2), third subparagraph, is received, the Agency shall adopt within 60 days a decision on the paediatric investigation plan considering all the updated reviews eventually conducted and of the initial decision in accordance with paragraphs 2 and 3.

5. Within time periods referred to in paragraphs 1, 2, 3 or 4 the Agency may request the applicant to propose modifications to the plan or ask for additional information, in which case the time-limits referred to in paragraphs 1, 2, 3 and 4 shall be extended for a maximum of the same number of days. These time-limits shall be suspended until the supplementary information requested has been provided.

6. The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency.

Article 78

Granting of a waiver

1. An applicant may, on the grounds set out in Article 75(1), apply to the Agency for a product-specific waiver.

2. Following the receipt of a valid application in accordance with the provisions of Article 76(2), the Agency shall within 90 days adopt a decision as to whether or not a product-specific waiver shall be granted.

Whenever appropriate, the Agency may request the applicant to supplement the particulars and documents submitted. Where the Agency avails itself of this option, the 90-day time-limit shall be suspended until such time as the supplementary information requested has been provided.

3. When appropriate, the Agency may of its own motion adopt decisions, on the basis of the grounds set out in Article 75(1), to the effect that a class or a product-specific waiver, as referred to in Article 75(2), should be granted.

4. The Agency may, at any time adopt a decision reviewing an already granted waiver.

5. If a particular product-specific or class waiver is revoked, the requirement set out in Article 6(5) of [revised Directive 2001/83/EC] shall not apply for 36 months from the date of its removal from the list of waivers.

6. The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency.

7. In consultation with the Commission **the national competent authorities,** and with interested parties, the Agency shall draw up and publish guidelines for the practical application of this Article.

Article 79

List of waivers

The Agency shall maintain a list of all waivers granted. The list shall be updated regularly and made available to the public.

Article 80

Waivers granted following a negative decision on a paediatric investigation plan

If, having considered a paediatric investigation plan, the Agency concludes that Article 75(1), points (a), (b) or (c), applies to the medicinal product concerned, it shall adopt negative a decision under Article 77, paragraphs 1, 2 or 4.

In such cases, the Agency shall adopt a decision in favour of a waiver under Article 78(3). The two decisions shall be adopted at the same time by the Agency.

The procedure laid down in Article 87 shall apply for the adoption of **a** decisions by the Agency.

Article 81

Deferrals

1. At the same time as the application for a paediatric investigation plan is submitted under Article 76(1) or during the assessment for a paediatric investigation plan, the applicant may also make a request for deferral of the initiation or completion of some or all of the measures set out in that plan. Such deferral shall be justified on scientific **or** ~~and~~ technical grounds or on grounds related to public health.

   In any event, a deferral shall be granted when it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population or when studies in the paediatric population will take longer to conduct than studies in adults.

2. The Agency shall adopt a decision on the request referred to in paragraph 1 and inform the applicant thereof. The Agency shall adopt such decision at the same time as the adoption of the positive decision under Article 77, paragraphs 1 or 2.

   A decision in favour of a deferral shall specify the time-limits for initiating or completing the measures concerned.

3. The length of the deferral shall be specified in a decision of the Agency and shall not exceed five years.

4. On the basis of the experience acquired as a result of the operation of this Article, the Commission is empowered to adopt delegated acts in accordance with Article 175 to amend the grounds for granting a deferral referred to in paragraph 1.

Article 82

Prolongation of deferrals

1. In duly justified cases, a request for a prolongation of the deferral, may be submitted, at least 6 months before the expiry of the deferral period. A prolongation of the **deferral** ~~derogation~~ shall not exceed the duration of the deferral period given under Article 81(3).

   The Agency shall decide on the prolongation within 60 days.

2. Whenever appropriate, the Agency may ask the applicant to submit**, within the deadline set by the Agency,** additional particulars and documents, in which case the time-limit of 60 days shall be suspended until the supplementary information requested has been provided.

3. The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency.

Article 83

Waivers during a public health emergency

1. The decision by the Agency referred to in Article 6(5), point (e) of [revised Directive 2001/83/EC] shall concern only medicinal products intended for the treatment, prevention or medical diagnosis of a serious or life-threatening disease or condition which are directly related to the public health emergency.

2. The decision mentioned under paragraph 1 shall include the grounds for providing such derogation and its duration.

3. At the latest at the date of expiry of the derogation referred to in paragraph 2, the applicant shall submit to the Agency a paediatric investigation plan or an application for a waiver with a request for agreement in accordance with the provisions of Article 76(1).

Article 84

Modification of a paediatric investigation plan

1. If, following the decision agreeing the paediatric investigation plan, the applicant encounters such difficulties with its implementation as to render the plan unworkable or no longer appropriate, the applicant may propose changes or request the Agency to issue a deferral in accordance with Article 81 or a waiver in accordance with Article 75. The Agency shall adopt within 90 days a decision on the basis of the procedure laid down in Article 87. When appropriate, the Agency may request the applicant to supplement the particulars and documents submitted. Where the Agency avails itself of this option, the time-limit shall be suspended until such time as the supplementary information requested has been provided.

2. If, following the decision agreeing the paediatric investigation plan referred to in Article 77, paragraphs 1, 2 and 4, or on the basis of the updated paediatric investigation plan received in accordance with Article 77(3), the Agency, on the base of new scientific information available, considers that the agreed plan or any of its elements are no longer appropriate, it shall request the applicant to propose changes to the paediatric investigation plan.

   The applicant shall submit the changes requested within 60 days.

   Within 30 days, the Agency **in consultation with Committee for Medicinal Products for Human Use and, as necessary, the relevant working parties established under Article 150.** shall review these changes and adopt a decision on their refusal or acceptance.

3. Within the time period referred to in paragraph 2, third subparagraph, the Agency may request the applicant for additional modifications to the submitted changes or to submit additional information, in those cases the time-limits referred to in paragraph 2, third subparagraph, shall be extended by another 30 days. This time-limit shall be suspended until the supplementary information requested or the additional modifications have been provided.

4. The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency.

Article 85

Detailed arrangements for applications in relation to paediatric investigation plans, waivers and deferrals

1. In consultation with the Member States, the Commission and interested parties, the Agency shall draw up the detailed arrangements concerning the format and content which applications for agreement or modification of a paediatric investigation plan, and requests for waivers or deferrals are to follow in order to be considered valid and concerning the operation of the compliance check referred to in Articles 48, 49(2) **of [revised Directive 2001/83/EC]. and Articles** ~~,~~ 86 and 90(2) **of this Regulation** ~~of [revised Directive 2001/83/EC]~~.

2. The detailed arrangement concerning the format and content of applications for agreement of a paediatric investigation plan mentioned in paragraph 1 shall:
   (a) specify which information should be included in an application for agreement or modification of a paediatric investigation plan or requests for a waiver in the cases referred to in Article 75(1);
   (b) be adapted to take into account the specificities of:
      (i) adapted procedure for paediatric investigation plans as referred to in Article 74(2);
      (ii) products intended to be developed only for use in children;
      (iii) products intended to be submitted under the procedure referred to in Article 92.

Article 86

Compliance with the paediatric investigation plan

Where the application is submitted in accordance with the procedures set out in in this Regulation, the Committee for Medicinal Products for Human Use shall verify whether an application for marketing authorisation or variation complies with the requirements laid down in Article 6(5) of [revised Directive 2001/83/EC].

Article 87

Procedure for adopting a decision in relation to paediatric investigation plans, a waiver or a deferral

1. Decisions referred to in Articles 77, 78, 80, 81, 82 and 84 adopted by the Agency shall be supported by scientific conclusions which shall be annexed to the decision.

2. ~~Where t~~**T**he Agency ~~considers it necessary, it may~~ **shall, where necessary,** consult the Committee for Medicinal Products for Human Use ~~or the appropriate working parties~~ when preparing the above mentioned scientific conclusions. **The Committee for Medicinal Products for Human Use shall ensure, as necessary, the appropriate involvement of the relevant scientific expertise through at least one the working parties established under Article 150.** The outcome of such consultations shall be annexed to the decision.

3. Decisions of the Agency shall be made public after deletion of any information of a commercially confidential nature.

Article 88

Discontinuation of a paediatric investigation plan

Where a paediatric investigation plan, agreed in accordance with the provisions of Article 77, paragraphs 1, 2 and 4, is discontinued, **in cases where the overall product development is stopped,** the applicant shall notify the Agency of its intention to discontinue the conduct of the paediatric investigation plan and provide the reasons for such discontinuation no less than six months before the discontinuation .
The Agency shall publish this information **after removing personal or commercially sensitive information**.

Article 89

Scientific advice for paediatric developments

Any legal or natural person developing a medicinal product intended for paediatric use ~~or intended for in utero treatment~~ may, prior to the submission of a paediatric investigation plan and during its implementation, request advice from the Agency on the design and conduct of the various tests and studies necessary to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population in accordance with Article 138(1), point (za). **The Agency shall consult the Committee for Medicinal Products for Human Use when preparing the above mentioned scientific advice. The Committee for Medicinal Products for Human Use shall ensure, as necessary, the appropriate involvement of the relevant scientific expertise in particular regarding paediatric medicinal products through at least one the working parties established under Article 150.**

The Agency shall provide advice under this Article free of charge.

Article 90

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 Regulation:
   (a) the results of all clinical studies conducted in compliance with an agreed paediatric investigation plan as referred to in Articles 6(5), point (a), of [revised Directive 2001/83/EC] shall be included **when appropriate** in the summary of product characteristics and, if appropriate, in the package leaflet; or
   (b) any agreed waiver as referred to in Articles 6(5), points (b) and (c) of [revised Directive 2001/83/EC], 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 Commission shall include within the marketing authorisation a statement indicating compliance of the application with the agreed completed paediatric investigation plan.

Article 91

Variation of marketing authorisations on the basis of paediatric studies

1. Any clinical study which involves the use in the paediatric population of a medicinal product covered by a marketing authorisation and is sponsored by the marketing authorisation holder, whether or not it is conducted in compliance with an agreed paediatric investigation plan, shall be submitted to the Agency or to the Member States **in** which ~~have previously~~ **the medicinal product is** authorised ~~the medicinal product concerned~~ within six months of completion of the studies concerned.

2. Paragraph 1 shall apply independent of whether or not the marketing authorisation holder intends to apply for a marketing authorisation of a paediatric indication.

3. When products are authorised in accordance with the provisions of this Regulation, the Commission may update the summary of product characteristics and package leaflet, and may vary the marketing authorisation accordingly.

Article 92

Paediatric use marketing authorisation

1. An application for a paediatric use marketing authorisation shall be submitted in accordance with Articles 5 and 6 and shall be accompanied by the particulars and documents necessary to establish quality, safety and efficacy in the paediatric population, including any specific data needed to support an appropriate formulation, pharmaceutical form, strength, route of administration and eventual administration device for the product, in accordance with an agreed paediatric investigation plan. The application shall also include the decision of the Agency agreeing the paediatric investigation plan concerned.

2. Where a medicinal product is or has been authorised in a Member State or in the Union, data contained in the dossier on that product may, where appropriate, be referred to, in accordance with Article 29 or Article 9 of [revised Directive 2001/83/EC], in an application for a paediatric use marketing authorisation.

3. The medicinal product in respect of which a paediatric use marketing authorisation is granted may retain the name of any medicinal product which contains the same active substance and in respect of which the same marketing authorisation holder has been granted authorisation for use in adults.

4. Submission of an application for a paediatric use marketing authorisation shall in no way preclude the right to apply for a marketing authorisation for other therapeutic indications.

Article 93

Rewards for products authorised under the paediatric use marketing authorisation procedure

Where a paediatric use marketing authorisation referred to in Article 92 is granted and includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the product shall benefit from independent data and marketing protection periods referred to in Articles 80 and 81 of [revised Directive 2001/83/EC].

Article 94

Paediatric clinical trials

1. The EU database created by Article 81 of Regulation (EU) No 536/2014 shall include clinical trials carried out in third countries which are:
   (a) contained in an agreed paediatric investigation plan;
   (b) submitted following the provisions of Article 91.

2. For the clinical trials mentioned in paragraph 1 which are conducted in third countries, the description of the following elements shall be entered into the EU database prior to the start of the trial by the clinical trial sponsor, the addressee of the Agency's decision on a paediatric investigation plan referred to in Article 77, or by the marketing authorisation holder as appropriate:
   (aa) clinical trial identification (including the title of the trial, the universal trial number, clinical trial registration number);
   (aaa) clinical trial sponsor details
   (a) the clinical trial protocol;
   (b) the investigational medicinal products used;
   (c) the therapeutic indications covered;
   (d) details of the trial population.

Irrespective of the outcome of a clinical trial within 6 months from the end of the trial the clinical trial sponsor, the addressee of the Agency's decision on a paediatric investigation plan or the marketing authorisation holder as appropriate, shall submit to the EU database a summary of the results of the trial **which** shall be uploaded in the database.

If for justified scientific reasons it is not possible to submit the summary of the result of the trial within 6 months it shall be submitted to the EU database at the latest within twelve months after the trial has ended. The justification for the delay needs also to be submitted in the EU database.

Where the clinical trial referred to in paragraph 1 has been conducted outside the Union, it shall have been conducted in accordance with principles equivalent to those of Regulation Regulation (EU) No 536/2014 as regards the rights and safety of the subject and the reliability and robustness of the data generated in the clinical trial.

Data submitted in an application dossier which do not comply with paragraphs 1 to 2 shall not be considered in the assessment of an application for authorisation.

3. In consultation with the Commission, Member States and interested parties, the Agency shall draw up guidance on the nature of the information referred to in paragraph 2.

4. On the basis of the experience acquired as a result of the operation of this Article, the Commission may adopt implementing acts in accordance with the examination procedure referred to in Article 173(2) to amend the details concerning clinical trials conducted in third countries to be submitted to the EU database and referred to in paragraph 2.

Article 95

European network

1. The Agency shall develop a European network of patient representatives, academics, medicines developers, investigators and centres with expertise in the performance of studies in the paediatric population.

2. The objectives of the European network shall be, inter alia, to discuss priorities in the clinical development of medicines for children, in particular in areas of unmet medical need, to coordinate studies relating to paediatric medicinal products, to build up the necessary scientific and administrative competences at European level, and to avoid unnecessary duplication of studies and testing in the paediatric population.

Article 96

Incentives for research in medicinal products for children

Paediatric medicinal products shall be eligible for incentives made available by the Union and by the Member States to support research into, and the development and availability of, paediatric medicinal products.

Article 97

Fees and Union contribution for paediatric activities

1. Where an application for a paediatric use marketing authorisation is submitted in accordance with the procedure laid down in Article 92, the amount of the reduced fees for the examination of the application and the maintenance of the marketing authorisation shall be fixed in accordance with Article 6 of [new fee Regulation[51]].

2. Assessments of the following by the Agency shall be free of charge:
   (a) applications for waivers;
   (b) applications for deferrals;
   (c) applications for paediatric investigation plans;
   (d) compliance with the agreed paediatric investigation plan.

[51] Regulation [XXX] of the European Parliament and of the Council on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council [OJ L X, XX.XX.XXXX, p. X].

3. The Union contribution provided for in Article 154 shall cover the work of the Agency, including the assessment of paediatric investigation plans, scientific advice and any fee waivers provided for in this Chapter, and shall support the Agency's activities under Articles 94 and 95.

Article 98

*Yearly reporting **on paediatric activities***

At least on an annual basis, the Agency shall make public:

(a) a list of the ~~companies~~ **entities** and of the products that have benefited from any of the rewards and incentives in this Regulation;

(b) the companies that have failed to comply with any of the obligations in this Regulation;

(c) the number of paediatric investigation plans agreed in accordance with Article 74;

(d) the number of waivers agreed, providing also a summary of their reasons;

(e) a list of deferrals agreed;

(f) the number of paediatric investigation plans completed;

(g) the **prolongations** ~~renewals~~ of the deferrals beyond five years and the detailed reasons provided as mentioned in Article 82;

(h) the scientific advice provided for the development of medicinal products addressed to children.

REVISED DIRECTIVE

Section 7

Specific requirements for paediatric medicinal products

Article 48

Compliance with the paediatric investigation plan

1. The competent authority of the Member State for which an application for marketing authorisation or variation of a marketing authorisation is submitted under the provisions of this Chapter or of the Chapter VIII, shall verify whether it complies with the requirements laid down in Article 6(5).

2. Where the application is submitted in accordance with the procedure set out in this Chapter, Sections 3 and 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, as referred to in Article 148 of [revised Regulation (EC) No 726/2004] may, in the following cases, be requested to give its opinion as to whether studies conducted by the applicant are in compliance with the agreed paediatric investigation plan as defined in Article 74 of [revised Regulation (EC) No 726/2004]:
   (a) by the applicant, prior to submitting an application for a marketing authorisation or for a variation of a marketing authorisation;
   (b) by the competent authority of the Member State, when validating an application for a marketing authorisation or 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 an opinion drawn up 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 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 86.

Article 49

Data deriving from a paediatric investigation plan

1. Where a marketing authorisation or a variation of a marketing authorisation, is granted in accordance with the provisions under this Chapter or of the provisions under Chapter VIII:
   (a) the results of all clinical studies, conducted in compliance with an agreed paediatric investigation plan as referred to in Article 6(5), point (a), shall be included in the summary of product characteristics and, if appropriate, in the package leaflet, or
   (b) any agreed waiver as referred to in Article 6(5), points (b) and (c), 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.

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 the provisions under this Chapter or of the provisions under Chapter VIII and which are protected either by a supplementary protection certificate under [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate, may be submitted under the procedure laid down in Articles **5** ~~41~~ and **6** ~~42~~.

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.

Article 59

Placing on the market of products with paediatric indications

Where medicinal products are authorised for a paediatric indication following completion of an agreed paediatric investigation plan and those medicinal products have already been marketed with other therapeutic indications, the marketing authorisation holder shall, within two years of the date on which the paediatric indication is authorised, place the medicinal product on the market taking into account the 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 these deadlines.

Article 60

Discontinuation of the placing on the market of paediatric products

If a medicinal product is authorised for a paediatric indication and the marketing authorisation holder has benefited from rewards or incentives under Article 86 of this Directive or Article 93 of [revised Regulation (EC) No 726/2004], and these 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 14.

The marketing authorisation holder shall inform the competent authorities 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 shall make this fact publicly available.

Revised Regulation

Article 2

Definitions

(2) 'designated orphan medicinal product' means a medicinal product ~~under development~~ which has been granted an orphan designation by a decision referred to in Article 64(4);

(3) 'orphan medicinal products' means a medicinal product which has been granted an orphan marketing authorisation referred to in Article 69;

(4) 'orphan medicin**al product**~~e~~ sponsor' means any legal or natural person, established in the Union, who submitted an application for or has been granted an orphan designation **for a medicinal product** by a decision referred to in Article 64(4);

(5) 'similar medicinal product' means a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication;

(7) 'significant benefit' means a clinically relevant advantage or a major contribution to patient care of an orphan medicinal product if such an advantage **as compared to existing satisfactory methods** or contribution benefits a substantial part of the target population;

(8) 'clinically superior' means that a medicinal product is shown to provide a significant therapeutic or diagnostic advantage above that provided by an orphan medicinal product in one or more of the following ways:

(a) greater efficacy than an authorised ~~medicinal~~ orphan medicinal product in a substantial part of the target population;

(b) greater safety than an authorised **orphan** medicinal product in a substantial part of the target population;

(c) in exceptional cases, where neither greater safety nor greater efficacy has been shown, demonstration that the medicinal product otherwise makes a major contribution to ~~diagnosis or to~~ patient care.

(11) 'paediatric use marketing authorisation' means a marketing authorisation granted in respect of a medicinal product for human use which is not protected by a supplementary protection certificate under Regulation (EC) No 469/2009 of the European Parliament and of the Council concerning the supplementary protection certificate for medicinal products[52] [OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate, covering exclusively therapeutic indications which are relevant for use in the paediatric population, or subsets thereof, including the appropriate strength, pharmaceutical form or route of administration for that product.

REVISED DIRECTIVE

Article 4

Definitions

(37) 'paediatric investigation plan' means a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population;

(38) 'paediatric population' means that part of the population aged between birth and 18 years;

(39) 'medicinal prescription' means any medicinal prescription issued by a professional person qualified to do so;

[52] 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).

4TH READING PACKAGE:

SHORTAGES AND SECURITY OF SUPPLY

Recitals

REVISED DIRECTIVE

(5) The essential aim of any rules governing the authorisation, manufacturing, supervision, distribution and use of medicinal products must be 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.

(53) A marketing authorisation holder should**, within the limits of its responsibility,** ensure the appropriate and continuous supply of a medicinal product throughout its lifetime **to wholesale distributors, pharmacies or persons authorised to supply medicinal products so that the needs of patients in the Member State in question are met** irrespective of whether that medicinal product is covered by a supply incentive or not.

(80) In the event of a risk to public health, the marketing authorisation holder or the competent authorities should be able to make urgent safety or efficacy restrictions on their own initiative. In such case, when the referral procedure is launched, any duplication of assessment should be avoided.

(87) For integral combination 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 product in terms of compliance of the medicinal product with the requirements of this Directive and the [revised Regulation(EC) No 726/2004] and should ensure coordination of the information flow between the sectors throughout the assessment procedure and the lifecycle of the medicinal product.

(89) In the interests 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 identify any natural or legal person from whom they have been supplied these substances. Therefore, procedures and systems should be placed to provide that information in case it should be necessary with the view of quality, safety or efficacy of medicinal products.

(111) 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 have the power 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 and rely on the outcome of inspections conducted by trusted third countries competent authorities. To preserve the effectiveness of the inspections, the competent authorities should have the possibility to perform joint inspections and also, where necessary, unannounced inspections.

REVISED REGULATION

(136) Shortages of medicinal products represent a growing threat to public health, with potential serious risks to **the smooth functioning of the internal market, as well as** the health of patients in the Union and impacts on the**ir** right ~~of patients~~ to access appropriate medical treatment**~~, as well as risks to the smooth functioning of the internal market~~**. The root causes of shortages are multifactorial, with challenges identified along the entire pharmaceutical value chain, from quality **and safety risks to** ~~and~~ manufacturing problems. In particular, shortages of medicinal products can result from supply chain disruptions and vulnerabilities affecting the supply of key ingredients and components. **Member States, depending on their situation, have addressed this in different ways. Due to ~~It can also result from~~ a lack of coordination ~~to~~ of measures taken at national level, these efforts resulted in a fragmented response leading to a jeopardy of the availability of medicines across the European Union.~~ ~~to adress risks to supply to cover the needs of patients in a given Member State.~~** ~~Therefore, all m~~**M**arketing authorisation holders should have shortage prevention plans in place **for certain products**, to prevent **or mitigate** shortages. The Agency should provide guidance to marketing authorisation holders on approaches to streamline the implementation of those plans.

(137) To achieve a better security of supply for medicinal products in the internal market and to contribute thereby to a high level of public health protection, it is appropriate to approximate the rules on monitoring and reporting of actual or potential shortages of medicinal products, including the procedures and the respective roles and obligations of concerned entities in this Regulation. It is important to ensure continued supply of medicinal products, which is often taken for granted across Europe. This is especially true for the most critical medicinal products which are essential to ensure the continuity of care, the provision of quality healthcare and guarantee a high level of public health protection ~~in Europe~~ **within the Union**.

(137a) **The phenomenon of parallel trade in medicinal products concerns medicinal products traded from one Member State to another Member State ~~or third country~~. Parallel trade facilitates the free movement of medicinal products due to the fact that the medicinal products are authorised in more Member States on the basis of the Union legislation. This situation is different from export, where the harmonised system of authorising and making medicinal products available on the market does not exist. While the Court of Justice has ruled that parallel trade fosters the free movement of medicinal products and is therefore beneficial to the internal market~~-~~, it has also recognised that the need to ensure that a country has reliable supplies for essential medical purposes, in particular a supply of medicinal products to the public that is reliable and of good quality, may, under Article 36 TFEU, justify a restriction on trade between Member States if that objective contributes to protecting human health and human life. Therefore, it should be possible for a Member State to require, for certain medicinal products, to ~~establish a system of notification~~ be informed by wholesale distributors whenever one of these products leaves the Member State in question to be distributed ~~elsewhere~~ in another Member State. On the basis of this ~~notification~~ information and ~~the~~ other information at its disposal, including shortage prevention plans, the Member State should be able to take measures to prevent or mitigate shortages and should notify to the Agency. These measures should also be appropriate and proportionate to such objectives and take into account that the principles of the free movement of goods are restricted only for the purpose of safeguarding public health, thus respecting the case law of the Court of Justice of the European Union and the Treaties, notably the provisions on free movement and competition. The ~~notification~~ information requirements set out in this Article do not affect existing obligations under Union law for the notification of technical regulations and technical barriers to the internal market, including those set out in Directive 2015/1535. It is important to recognise that parallel import can contribute to the objective of access to medicines, notably in smaller or vulnerable markets.**

(138) The national competent authorities should be empowered to monitor shortages of medicinal products that are authorised through both national and centralised procedures, based on notifications of marketing authorisation holders. The Agency should be empowered to monitor shortages of medicinal products that are authorised through the centralised procedure, also based on notifications of marketing authorisation holders. **To ensure continuity of supply and availability of critical medicinal products on the market of any Member State where the medicinal product is authorised, rules for the transfer of the marketing authorisation or for the offer of a letter of access prior to the ~~permanent~~ withdrawal of the marketing ~~cessation~~ authorisation or the permanent market cessation, respectively, in ~~all~~ Member States where the marketing authorisation is valid, should be laid down. Such transfer should not be considered to be a variation. Rules on wholesale distribution of medicinal products, marketed as a result of a marketing authorisation, whose data have been shared via a letter of access, do not affect the contractual arrangements between the marketing authorisation holders or wholesalers concerned. ~~Such contractual arrangements may for example preclude the distribution of the medicinal product authorised under the access letter in Member States where the reference medicinal product is marketed.~~** When critical shortages are identified, both national competent authorities and the Agency should work in a coordinated manner to manage those critical shortages, whether the medicinal product concerned by the critical shortage is covered by a centralised marketing authorisation or a national marketing authorisation. Marketing authorisation holders and other relevant entities ~~must~~ **should** provide the relevant information to inform the monitoring. Wholesale distributors and other persons or legal entities, including patient organisations or health care professionals, may also report a shortage of a given medicinal product marketed in the Member State concerned to the competent authority. The Executive Steering Group on Shortages and Safety of Medicinal Products ('the Medicines Shortages Steering Group' (MSSG)) already established within the Agency pursuant to Regulation (EU) 2022/123 of the European Parliament and of the Council, should ~~adopt~~ **propose** a list of critical shortages of medicinal products and ensure monitoring of those shortages by the Agency**, to be adopted by the Commission**. The MSSG should also ~~adopt~~ **propose** a list of critical medicinal products authorised in accordance with [revised Directive 2001/83/EC] or this Regulation to ensure monitoring of the supply of those products**, to be adopted by the Commission**. The MSSG may provide recommendations on measures to be taken by marketing authorisation holders, the Member States, the Commission and other entities to resolve any critical shortage or to ensure the security of supply of those critical

medicinal products to the market. ~~Implementing acts can be adopted by the Commission to ensure that appropriate measures, including the establishment or maintenance of contingency stocks, are taken by marketing authorisation holders, wholesale distributors or other relevant entities~~ **~~of critical medicines identified by using the common methodology~~.**

(138a) Monitoring and prevention activities, together with targeted actions at national level, have at times proven to be insufficient to prevent disruption of supply within the Union of critical medicinal products. Experience has shown that difficulties in the supply chain have led to uncoordinated approaches at company and ~~regulatory~~ governmental level, such as imposing contingency stock requirements on actors in the supply chain, which led to restrictions in the internal market. Such restrictions are also likely to result in a suboptimal ~~flow~~ level of ~~aecess~~ availability of ~~to~~ critical medicines, due to the fact that a fragmented approach is jeopardising the availability throughout the European Union. It is necessary to ensure that tools for a Union approach are available to address such situations which are likely to lead to such restrictions, in specific circumstances, to ensure the free movement of medicines by safeguarding security of a safe and stable supply of them at Union level. The Commission should therefore be empowered to adopt implementing acts, after having duly identified a serious risk of disruptions and having considered the appropriateness and proportionality of the intervention, notably as regards its impact on fundamental rights, laying down measures of last resort to improve security of supply within the Union. These should be limited to the establishment of temporary criteria to be applied by Member States when the arising of shortages creates a tangible risk of fragmentation across the Union supply chains. ~~ensuring appropriate contingency stock levels and appropriate supplies of critical medicinal products to wholesale distributors healthcare systems. While disruptions regarding centrally authorised products can be better addressed by to different actors within the supply chain, measures concerning nationally authorised medicinal products should only be addressed to Member States.~~

(139) ~~To ensure continuity of supply and availability of critical medicinal products to the market, rules on the transfer of the marketing authorisation prior to the permanent marketing cessation should be laid down. Such transfer should not be considered to be a variation.~~

(140) It is recognised that improved access to information contributes to public awareness, gives the public the opportunity to express its observations and enables authorities to take due account of those observations. The general public should therefore have access to information in the Union Register of medicinal products, the Eudravigilance database and the manufacturing and wholesale distribution database, after the deletion of any commercially confidential information by the competent authority. Regulation (EC) No 1049/2001 of the European Parliament and of the Council[53] gives the fullest possible effect to the right of public access to documents and lays down the general principles and limits on such access. The Agency should therefore give the widest possible access to the documents while carefully balancing the right for information with existing data protection requirements. Certain public and private interests, such as personal data and commercially confidential information, should be protected by way of exception in accordance with Regulation (EC) No 1049/2001.

(141) To ensure the enforcement of certain obligations relating to the marketing authorisation for medicinal products for human use granted in accordance with this Regulation, the Commission should be able to impose financial penalties. When assessing the responsibility for failures to comply with those obligations and imposing such penalties, it is important that means exist to address the fact that marketing authorisation holders could be part of a wider economic entity. Otherwise, there is a clear and identifiable risk that the responsibility for a failure to comply with those obligations could be evaded, which might have an impact on the ability to impose effective, proportional and dissuasive penalties. The penalties imposed should be effective, proportionate and dissuasive, having regard to the circumstances of the specific case. For the purposes of ensuring legal certainty in the conduct of the infringement procedure, it is necessary to set maximum amounts for penalties. Those maximum amounts should not be linked to the turnover of a particular medicinal product but the economic entity involved.

[53] Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents (OJ L 145, 31.5.2001, p. 43).

Article 16

Marketing authorisations

4. After a marketing authorisation has been granted, the marketing authorisation holder shall inform the Agency of the dates of actual marketing of the medicinal product for human use in the Member States, taking into account the various presentations authorised.

~~The marketing authorisation holder shall notify the Agency and the competent authority of the Member State concerned of the following:~~

~~(a) its intention to permanently cease the marketing of a medicinal product in that Member State in accordance with Article 116(1), point (a); or~~

~~(b) its intention to temporarily suspend the marketing of a medicinal product in that Member State in accordance with Article 116(1), point (c); or~~

~~(c) a potential or actual shortage in that Member State in accordance with Article 116(1), point (d); and~~

~~its reasons for such action under points (a) and (b) in accordance with Article 24, as well as any other reason relating to precautionary actions with regard to quality, safety, efficacy and the environment.~~

Upon request by the Agency, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the Agency with all data relating to the volume of sales of the medicinal product at Union level, broken down by Member State, and any data in the marketing authorisation holder's possession relating to the volume of prescriptions in the Union and its Member States.

Article 24

Suspension of marketing, withdrawal from the market of a medicinal product, withdrawal of a marketing authorisation by the marketing authorisation holder

1. ~~In addition to the notification made pursuant to Article 116, T~~**T**he marketing authorisation holder shall notify the Agency without undue delay of any action they take 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 if such action is based on the following grounds:

   (a) the medicinal product is harmful;
   (b) it lacks therapeutic efficacy;
   (c) the benefit-risk balance is not favourable;
   (d) its qualitative and quantitative composition is not as declared;
   (e) the controls on the medicinal product or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled; or
   (f) a serious risk to the environment or to public health via the environment has been identified and not sufficiently addressed by the marketing authorisation holder.

   Where the action referred to in the first subparagraph is to withdraw a medicinal product from the market, the marketing authorisation holder shall provide information on the impact of such withdrawal on patients who are already being treated.

   ~~The notification of the permanent withdrawal of a medicinal product from the market or of the temporary suspension of the marketing authorisation, or of the permanent withdrawal of a marketing authorisation or of the temporary disruption in supply of a medicinal product shall be made in accordance with Article 116(1).~~

The marketing authorisation holder shall make the notification electronically and in the formats made available by the Agency. The Agency shall consult the Member States when drawing up the formats.

2. The marketing authorisation holder shall make the notification pursuant to paragraph 1 if the action is taken in a third country and such action is based on any of the grounds set out in **paragraph 1**~~Articles 195 or 196(1) of [revised Directive 2001/83/EC]~~.

3. In the cases referred to in paragraphs 1 and 2, the Agency shall forward the information to the competent authorities of the Member States without undue delay.

~~4. Where the marketing authorisation holder intends to permanently withdraw the marketing authorisation for a critical medicinal product, the marketing authorisation holder shall, prior to the notification referred to in paragraph 1, offer, on reasonable terms, to transfer the marketing authorisation to a third party that has declared its intention to place that critical medicinal product on the market, or to use the pharmaceutical non-clinical and clinical documentation contained in the file of the medicinal product for the purposes of submitting an application in accordance with Article 14 of [revised Directive 2001/83/EC].~~

CHAPTER X

AVAILABILITY AND SECURITY OF SUPPLY OF MEDICINAL PRODUCTS

SECTION 1

MONITORING AND MANAGEMENT OF SHORTAGES AND CRITICAL SHORTAGES

Article 115a

Derogations on the provisions of this chapter

1. Member States may waive the application of Articles 116(3a), 117~~(3) point a~~, Articles 120(2), 121(5a), 127(4), 129, 130(2) point c, 130(4) point c ~~within their territory~~, ~~insofar as the marketing authorisation holders subject to those rules supply~~ when the medicinal products are supplied for military or defence purposes or insofar as the application of such requirements imply a risk to national security and defense.

1a. Member States may exempt authorities within their territory of the obligation to communicate information in accordance with Articles 121 and 127 insofar as such requirements imply a risk to national security and defense.

2. Member States may exempt a marketing authorisation holder in possession of a marketing authorisation for a medicinal product authorised in that Member State in accordance with article 205 of [revised Directive 2001/83/EC] ~~of~~ from complying with the obligations set out in the articles 116, 117, 119, 125, 128 and 133.

Article 116

Marketing authorisation holder notifications

1. **In addition to the rules on notification referred to in Article 24 of this Regulation and Article 203~~(3)~~ of [the revised Directive 2001/83/EC]** ~~T~~**t**he marketing authorisation holder of a medicinal product in possession of a centralised marketing authorisation or a national marketing authorisation (**these are referred to in this chapter as**'the marketing authorisation holder') shall notify the competent authority of the Member State where the medicinal product has been placed on the market and, in addition, the Agency for a medicinal product covered by a centralised marketing authorisation (these are referred to in this Chapter as 'the competent authority concerned') of the following:
   (a) its decision to permanently cease the marketing of a medicinal product in that Member State no less than twelve months before the last supply of that medicinal product into the market of a given Member State by the marketing authorisation holder;
   (b) its request to permanently withdraw the marketing authorisation for that medicinal product authorised in that Member State no less than twelve months before the last supply of that medicinal product into the market of a given Member State by the marketing authorisation holder;
   (c) its decision to temporarily suspend the marketing of a medicinal product in that Member State no less than six months before the start of the temporary suspension of supply of that medicinal product into the market of a given Member State by the marketing authorisation holder;
   (d) a temporary disruption in supply of a medicinal product in a given Member State, of an expected duration of in excess of **two weeks** ~~two weeks or,~~ based on the demand forecast of the marketing authorisation holder**, as soon as possible and in any event** no less than **three**~~six~~ months before the start of such temporary disruption of supply ~~or, if this is not possible and where duly justified, as soon as they become aware of such temporary disruption, to allow the Member State to monitor any~~ **expected** ~~potential or actual shortage in accordance with Article 118(1)~~.

~~(e)~~ By way of derogation to paragraph 1, point (d), the marketing authorisation holder shall notify the temporary disruption in supply of a medicinal product in a given Member State as soon as they become aware of such temporary disruption where exceptional circumstances, which shall be duly identified and substantiated to the competent authority concerned, prevented the marketing authorisation holder from complying with the deadlines laid down therein.

~~(f)~~ The marketing authorisation holder shall make the notification electronically and in the formats made available by the Agency. The Agency shall consult the Member States when drawing up the formats.

2. For the purposes of the notification made in accordance with paragraph 1, points (a), (b) and (c), the marketing authorisation holder shall provide the information set out in Part I of Annex IV.

   For the purpose of notifications made in accordance with the paragraph 1, point (d), the marketing authorisation holder shall provide the information set out in Part III of Annex IV. The marketing authorisation holder shall immediately notify the competent authority concerned, as appropriate, of any relevant changes to the information provided according to this paragraph.

3. The Commission is empowered to adopt delegated acts, in accordance with Article 175 in order to amend Annex IV as regards the information to be provided in case of a temporary disruption of supply, information to be provided in case of a suspension or cessation of marketing of a medicinal product or withdrawal of the marketing authorisation of a medicinal product, or the content of the shortage prevention plan referred to in Article 117.

3a. Where the marketing authorisation holder intends to withdraw the marketing authorisation ~~for~~ or permanently cease to market in ~~all~~ a Member States ~~s~~ where the marketing authorisation is valid for a critical medicinal product identified by the competent authority of a Member State pursuant to Article 127(1), ~~or~~ medicinal products identified in accordance with 126(2a) or a priority antimicrobial pursuant to Article 40 (3) ~~using the methodology pursuant to Article 130(1), point a~~, the marketing authorisation holder shall, prior to the notification referred to in Article 116(1), point b:

(a) publish a declaration of its intention to offer to transfer the marketing authorisation or its intention to issue a letter of access as referred to in Article 14 of [revised Directive 2001/83] via a dedicated webpage on its website and communicate the electronic link to such webpage to the competent authority of the Member State and the Agency. The Agency shall publish and compile a list of such electronic links.

(b) offer, on reasonable terms, to transfer the marketing authorisation or the letter of access to a third party that has declared its intention to place that critical medicinal product identified using the methodology pursuant to Article 130 (1), point (a) on the market, or to allow the use of the pharmaceutical non-clinical and clinical documentation contained in the file of that critical medicinal product for the purposes of submitting an application in accordance with Article 14 of [revised Directive 2001/83/EC].

(c) inform the competent authority concerned on the outcome of the negotiations with the third party or parties.

For the purpose of this paragraph, the marketing authorisation holder shall provide as part of the notification referred to in article 116 (1) point (b) information proving that they have taken steps to make the marketing authorisation available to third parties on reasonable terms.

Article 117

The shortage prevention plan

1. The marketing authorisation holder ~~as defined in Article 116(1)~~ shall have in place and keep up to date a shortage prevention plan for any **critical** medicinal product **identified by the competent authorities of a Member State in accordance with Article 127(1) and for medicinal products identified in accordance with Article 126 (2a).** ~~**on the Union list of critical medicinal products.** placed on the market.~~ To put in place the shortage prevention plan, the marketing authorisation holder shall include the minimum set of information set out in Part V of Annex IV and take into account the guidance drawn up by the Agency according to paragraph 2.

The Agency, in collaboration with the working party referred to in Article 121(1), point (c), shall draw up guidance for marketing authorisation holders to put in place the shortage prevention plan. The guidance shall, in particular, indicate the relevant type and detail of information for the shortage prevention plan according to the different level of risk, including ~~**information**~~ **descriptions of** ~~**on**~~ **the relevant shortage management measures.**

~~**1a. In addition to paragraph 1, the competent authority of the Member State may, on public health grounds or and taking into account MSSG recommendations as referred to in Article 123 paragraph 4a, request the marketing authorisation holder of an authorised medicinal product placed on its market and which is not included in the Union list of critical medicinal products but identified by the Member State as of critical importance using the methodology set out in Article 130(1), point (a) to have in place a shortage prevention plan. iIn such cases, the timeline referred to in paragraph 1b shall apply.**~~

1~~b~~a. When a medicinal product is identified as critical ~~added to the Union list of critical medicinal products~~ pursuant to Article ~~131~~127, paragraph ~~3~~1, and when medicinal products are identified in accordance with Article 126 (2a) the marketing authorisation holder shall put in place the shortage prevention plan within ~~12~~ 3 months ~~from the addition of that product to the Union list of critical medicinal products~~. The shortage prevention plan shall be drawn up in accordance with paragraph 1.

1~~e~~b. Whenever a medicinal product is subject to a shortage prevention plan in accordance with this Article, the national competent authority ~~of the Member State~~ or the Agency may request the marketing authorisation holder to submit that shortage prevention plan at any time. The marketing authorisation holder shall submit that copy at the latest two days after receipt of such request.

~~2. The Agency, in collaboration with the working party referred to in Article 121(1), point (c), shall draw up guidance to marketing authorisation holders as defined in Article 116(1) to put in place the shortage prevention plan.~~

3. Where relevant, the marketing authorisation holder ~~as defined in Article 116(1)~~ shall update the shortage prevention plan to include additional information, ~~based on~~ **taking into account** recommendations of ~~**the competent authority of the Member State in case of a nationally authorized medicinal product, or of**~~ the Executive Steering Group on Shortages and Safety of Medicinal Products (also referred to as the Medicine Shortages Steering Group – 'MSSG', established in Article 3(1) of Regulation (EU) 2022/123, in accordance with Articles 123(4) and 132(1).

ANNEX IV

Part V

The shortage prevention plan

The Shortage Prevention Plan referred to in Article 117 shall contain the following minimum set of information:

(1) Product details:

(a) Product name;

(b) Active substance(s) and active substance manufacturer(s);

(c) Finished product manufacturer;

(d) ATC code;

(e) Therapeutic indication(s);

(f) Pharmaceutical form;

(g) Strength(s);

(h) Route(s) of administration;

~~(i) Pack size(s);~~

(j) Details of authorisation: procedure type (national (including Member State(s) involved)/ centralised marketing authorisation) and ~~reference~~**marketing authorisation number**;

(k) Member States in which the product is placed on the market.

(2) Shortage prevention measures and supply chain risk assessment:

(a) **Patient impact of potential sup~~ves~~ply disruptions, considering therapeutic indication and a~~A~~**lternative marketed medicinal products **and estimated market share by Member states in the previous 12 months**;

(b) Supply chain **risk assessment** ~~map, with risk identification and analysis with particular attention to supply chain vulnerabilities;~~**, to include:**

(i) Supply chain map, with particular attention to supply chain vulnerabilities;

(ii) A record of root causes of resolved shortages and mitigation measures taken for those shortages;

(ba) Final risk classification (low, medium, high) covering both the risk of shortage and its public health impact, with separate risk classification if necessary.

(2a)~~(c)~~ Shortage management measures, to include:

(a)~~(i)~~ a risk control strategy in place, to include information on strategies to minimise risks of shortages and how these are implemented;

(b)~~(ii)~~ a process for the detection and notification of supply disruptions and

(c)~~(iii)~~ a record of root causes of resolved shortages and mitigation measures taken for those shortages.

(2b)~~(d)~~ Process for check of effectiveness, review and update of the shortage prevention plan.

(3) Contact details

(a) Marketing authorisation holder name and address;

(b) Name and details of contact person.

Article 118

Shortage monitoring by the competent authority of the Member State or the Agency

1. Based on the reports referred to in Articles 120(1) and 121(1), point (c), information referred to in Articles 119, 120(2) and 121 and the notification made pursuant to Article 116(1), points (a) to (d) **and 120(1a)**, the competent authority concerned as referred to in Article 116(1) shall continuously monitor any **expected** ~~potential~~ or actual shortage of those medicinal products. **In addition, the competent authority concerned may use information contained in the repositories in Article 67(2), second subparagraph, point (e), of [revised Directive 2001/83/EC] or in a national repository.**

The Agency shall carry out that monitoring in collaboration with the relevant competent authority of the Member State whe**re**~~n~~ those medicinal products are authorised under this Regulation **or when coordinated EU action is required**.

2. For the purposes of paragraph 1, the competent authority concerned ~~as defined in Article 116(1)~~ may request any ~~additional~~ information from the marketing authorisation holder ~~as defined in Article 116(1)~~. In particular, it may request the marketing authorisation holder to submit a shortage mitigation plan in accordance with Article 119(2), a risk assessment of impact of suspension, cessation or withdrawal in accordance with Article 119(3), or the shortage prevention plan referred to in Article 117. The competent authority concerned may set a deadline for the submission of the information requested.

Article 2

Definitions

(14) 'shortage' means a situation in which the supply of a medicinal product that is authorised and placed on the market in a Member State does not meet the demand for that medicinal product in that Member State.

Article 119

Obligations on the marketing authorisation holder

1. The marketing authorisation holder ~~as defined in Article 116(1)~~ shall:
   (a) submit the information requested in accordance with Article 118(2)**,** ~~or~~ Article 124(2), point (b)**, or Article 117(1be), 2nd subparagraph** to the competent authority concerned ~~as defined in Article 116(1)~~, without undue delay, using the tools, methods of and criteria for the monitoring and reporting established pursuant to Article 122(4), point (b), by the deadline set by that competent authority;
   (b) provide updates to the information provided in accordance with point (a), where necessary;

(c) justify any failure to provide any of the requested information;

(d) where necessary, submit a request to the competent authority concerned ~~as defined in Article 116(1)~~ for an extension of the deadline set by that competent authority in accordance with point (a), and

(e) indicate whether the information provided in accordance with point (a) contains any commercially confidential information, identify the relevant parts of that information having a commercially confidential nature and explain why that information is of such nature.

2. To prepare the shortage mitigation plan referred to in Article 118(2), the marketing authorisation holder ~~as defined in Article 116(1)~~ shall include the minimum set of information set out in Part IV of Annex IV and take into account the guidance drawn up by the Agency according to Article 122(4), point (c).

3. To prepare a risk assessment of impact of suspension, cessation or withdrawal referred to in Article 118(2), the marketing authorisation holder ~~as defined in Article 116(1)~~ shall include the minimum set of information set out in Part II of Annex IV and take into account the guidance drawn up by the Agency according to Article 122(4), point (c).

(3a) In case of medicinal products that are not subject to the obligation of preparing a shortage prevention plan the marketing authorisation holder shall carry out a regular documented risk assessment of potential supply chain risks and, where necessary, take mitigating measures ~~in order to fulfil its obligations set out in Article 56, paragraph 3 of the [Revised Directive 2001/83/EC].~~

4. The marketing authorisation holder ~~as defined in Article 116(1)~~ shall be responsible for providing correct, not misleading, and complete information as requested by the competent authority concerned.

5. The marketing authorisation holder ~~as defined in Article 116(1)~~ shall cooperate with that competent authority and disclose, on their own motion, any relevant information to that authority and update the information as soon as new information becomes available.

Article 120

Obligations on other actors

1. Wholesale distributors and other persons or legal entities that are authorised or entitled to supply medicinal products authorised to be placed on the market of a Member State pursuant to Article 5 of [revised Directive 2001/83/EC] to the public may report a shortage of a given medicinal product marketed in the Member State concerned to the competent authority in that Member State.

1a. Member States may require for centrally or nationally authorised medicinal products, that a~~A~~ wholesale distributor that is not the marketing authorisation holder who intends to distribute the medicinal product to another Member State ~~and whose intention it is to obtain a medicinal product from a Member State ('source Member State') and to distribute this medicinal product in another Member State or third country ('destination Member State) or third country notifies~~ informs the competent authority of the source Member State of this intention. This ~~notification~~ information shall include:

(a) The name of the medicinal product and authorisation number;

(b) Active substance(s);

(c) Pharmaceutical form;

(d) Strength;

(e) Pack size

(f) The quantity of the medicinal product ~~obtained~~/which ~~is or~~ shall be ~~obtained~~ ~~in~~taken out from the source Member State;

(g) Destination Member State ~~or third country of destination~~.

~~When a Member State adopts a measure referred to in the first subparagraph, it shall notify the Commission together with the justification in accordance with the fourth subparagraph.~~

Based on the information ~~notification made~~ provided by the wholesaler ~~referred to in this paragraph~~ and on the information available pursuant to this Chapter, the source Member State may take measures to prevent or to mitigate shortages in the source Member State. ~~In addition to the requirements pursuant Directive 2015/1535,~~ T~~t~~he Member State shall notify the Agency of the measures referred to in this subparagraph.

The ~~measures notification~~ information requirement referred to in the first subparagraph and measures referred to in the ~~second~~third subparagraph ~~referred to in this paragraph adopted by the source Member State for medicinal products intended for distribution to a destination Member State~~ 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 Treaty rules.

2. For the purposes of Article 118(1), where relevant, upon request from the competent authority concerned ~~as defined in Article 116(1)~~, entities including other marketing authorisation holders ~~as defined in Article 116(1)~~, importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public shall provide any information requested ~~in a timely manner~~ **within the timeframe specified by the competent authority concerned**.

Article 121

Role of the competent authority of the Member State

1. The competent authority of the Member State shall:
   (a) assess the merits of each confidentiality claim made by the marketing authorisation holder ~~as defined in Article 116(1)~~ in accordance with Article 119(1), point (e), and shall protect information which that competent authority considers to be commercially confidential against unjustified disclosure;

(b) publish information on actual shortages of medicinal products, in cases in which that competent authority has assessed the shortage, on a publicly available website;

(c) report to the Agency, through the single point of contact working party referred to in Article 3(6) of Regulation (EU) 2022/123, any shortage of a medicinal product that it identifies as a critical shortage in that Member State ~~to the Agency~~ without undue delay.

2. Following the reporting referred to in paragraph 1, point (c), and to facilitate the monitoring referred to in Articles 118(1), the competent authority of the Member State shall, through the working party referred to in paragraph 1, point (c):

(a) submit to the Agency the information referred to in Articles 122(1) or 124(2), point (a), using the tools, methods of and criteria for the monitoring and reporting established pursuant to Article 122(4), point (b), by the deadline set by the Agency;

(b) where necessary, provide updates to the information provided in accordance with point (a) to the Agency;

(c) justify any failure to provide any of the information referred to in point (a) to the Agency;

(d) where necessary, submit a request to the Agency to extend the deadline set by the Agency referred to in point (a);

(e) indicate whether the marketing authorisation holder ~~as defined in Article 116(1)~~ has indicated the existence of any commercially confidential information and provide the marketing authorisation holder's explanation of why that information is of a commercially confidential nature, in accordance with Article 119(1), point (e);

(f) inform the Agency of any actions foreseen or taken by that Member State to mitigate the shortage at national level.

3. Where the competent authority of the Member State has any information in addition to the information to be provided pursuant to this Article, it shall immediately provide such information to the Agency through the working party referred to in paragraph 1, point (c).

4. Following the addition of a medicinal product on the list of critical shortages of medicinal products referred to in Article 123(1), the competent authority of the Member State shall, through the working party referred to in paragraph 1, point (c), provide any information requested pursuant to Article 124(2), point (a), to the Agency.

5. Following any MSSG recommendations provided in accordance with Article 123(4), the competent authority of the Member State shall, through the working party referred to in paragraph 1, point (c):
   (a) report to the Agency on any information received from the marketing authorisation holder ~~as defined in Article 116(1)~~ of the medicinal product concerned or from other actors pursuant to Article 120(2);
   (b) ~~comply and~~ coordinate with any **relevant** measures taken by the Commission ~~pursuant to Article 126(1), point (a)~~;
   (c) take into account any MSSG recommendations referred to in Article 123(4);
   (d) inform the Agency of any actions foreseen or taken by that Member State in accordance with points (b) and (c) and report on any other actions taken to mitigate or resolve the critical shortage in the Member State, as well as the results of these actions.

5a. The competent authority of the Member State may require wholesale distributors and other persons or legal entities that are authorised or entitled to supply to the public medicinal products authorised to be placed on the market of a Member State pursuant to Article 5 of [revised Directive 2001/83/EC] to report a shortage of a medicinal product marketed in the Member State concerned.

6. The Member States may request that the MSSG provide further recommendations **pursuant to**~~, referred to in~~ Article 123(4).

Article 2

Definitions

(15) 'critical shortage in the Member State' means a shortage of a medicinal product **which**~~,~~ **may results~~ in a significant impact on the healthcare system of a Member State or results in harm or risk of harm to patients and for which** there is no appropriate alternative medicinal product available **in sufficient quantities** on the market in that Member State~~, and that shortage cannot be resolved.~~

Article 122

Role of the Agency concerning shortages

1. For the purposes of Article 118(1), the Agency may request additional information from the competent authority of the Member State, through the working party referred to in Article 121(1), point (c). The Agency may set a deadline for the submission of the information requested.

2. On the basis of Article 118(1), the Agency, in collaboration with the working party referred to in Article 121(1), point (c), shall identify **critical shortages of Union concern.**~~the medicinal products for which the shortage cannot be resolved without EU coordination.~~

3. The Agency shall inform the MSSG of the shortages of the medicinal products that have been identified pursuant to paragraph 2.

4. For the purposes of fulfilling the tasks referred to in Articles 118(1), 123 and 124, the Agency shall ensure the following, in consultation with the working party referred to in Article 121(1), point (c):
   (a) set ~~the criteria~~**guidelines** to **support the implementation~~ing acts on~~** ~~adopt and review the list of critical shortages~~ **~~of Union concern~~** ~~referred to in~~**of** Article 123(1) **and (2)**;

(b) specify the tools, including the European Shortages Monitoring Platform ('ESMP'), established by Regulation (EU) 2022/123, once the scope is expanded pursuant to paragraph 6, the methods of and criteria for the monitoring and reporting provided for in Articles 119(1), point (a), and 121(2), point (a);

(c) draw up guidance to allow marketing authorisation holders ~~as defined in Article 116(1)~~ to put in place the risk assessment of impact of suspension, cessation or withdrawal and the shortage mitigation plan as referred to in Article 118(2);

(d) specify the methods for the provision of recommendations referred to in Article 123(4);

(e) publish information covered by points (a) to (d) on a dedicated webpage on its web-portal referred to in Article 104.

5. For the duration of the critical shortage **of Union concern** and until the MSSG considers it to be resolved, the Agency shall regularly report on the results of the monitoring referred to in Article 124 to the Commission and the MSSG, and in particular, it shall report any event that is likely to lead to a major event, as defined in Article 2 of Regulation (EU) 2022/123. Where a public health emergency is recognised in accordance with Regulation (EU) 2022/2371 or an event is recognised as a major event, in accordance with Regulation (EU) 2022/123, that Regulation ~~applies~~**prevails**.

6. For the purposes of implementing this Regulation, the Agency shall expand the scope of the ESMP. The Agency shall ensure that, where relevant, data is interoperable between the ESMP, Member States' IT systems and other relevant IT systems and databases, ~~without~~ **while avoiding** duplication of reporting.

Article 123

Role of the MSSG and the list of critical shortages ~~***of Union concern***~~ *of medicinal products* ***of Union concern***

1. Based on the monitoring referred to in Article 118(1), and following consultation with the Agency and the working party referred to in Article 121(1), point (c), the MSSG shall ~~adopt~~ **recommend to the Commission** a list of critical shortages **of Union concern** of medicinal products authorised to be placed on the market of a Member State pursuant to Article 5 of [revised Directive 2001/83/EC]and for which co-ordinated Union level action is necessary ('the list of critical shortages of medicinal products **of Union concern**').

2. The MSSG shall review the status of the critical shortage **of Union concern** whenever necessary and shall **recommend the Commission to** update the list when it considers that a medicinal product needs to be added or that the critical shortage **of Union concern** has been resolved based on the report pursuant to Article 122(5).

2a. Considering the recommendation of the MSSG, the Commission shall, by means of an implementing act, adopt the list of critical shortages of medicinal products of Union concern.

3. In addition, the MSSG shall amend its rules of procedure, and the rules of procedure of the working party referred to in Article 121(1), point (c), in accordance with the roles set out in this Regulation.

4. The MSSG may provide recommendations on measures to resolve or to mitigate the critical shortage **of Union concern**, in accordance with the methods referred to in Article 122(4), point (d), to relevant marketing authorisation holders, the Member States, the Commission, **the Agency,** the representatives of healthcare professionals or other entities.

4a. **The MSSG ~~may also~~ shall provide recommendations to the Commission ~~to Member States~~ regarding the possibility, pursuant to article 117 paragraph 1a, to require a shortage prevention plan for a medicinal product that is not a critical medicinal product identified in accordance with Article 127, paragraph 1. In doing so, the MSSG shall take into account the criteria set out in Article 126, paragraph 2a. ~~on the Union list of critical medicinal products.~~**

Article 2

Definitions

(16) 'critical shortage **of Union concern**' means a critical shortage in the Member State **that cannot be resolved at Member State level and** for which coordinated Union level action is ~~considered~~ necessary to resolve that shortage in accordance with this Regulation.

Article 124

*Management of the critical shortage **of Union concern***

1. Following the addition of a medicinal product to the list of critical shortages **of Union concern** pursuant to Article 123, paragraphs 1 and 2, and based on the continuous monitoring carried out in accordance with Article 118(1), the Agency, in coordination with the competent authority of the Member State **concerned**, shall continuously monitor the critical shortage **of Union concern** of that medicinal product.

2. For the purposes of paragraph 1, ~~where that information is not already available to the Agency~~, the Agency may**, if that information is not already available to the Agency,** request relevant information on that critical shortage **of Union concern** from:
   (a) the competent authority of the Member State concerned through the working party referred to in Article 121(1), point (c);
   (b) the marketing authorisation holder ~~as defined in Article 116(1)~~;
   (c) the other actors listed in Article 120(2).

   For the purposes of this paragraph, the Agency may set a deadline for the submission of the information requested.

3. The Agency shall establish within its web-portal referred to in Article 104 a publicly available webpage that provides information on actual critical shortages **of Union concern** of medicinal products in cases in which the Agency has assessed the shortage and has provided recommendations to healthcare professionals and patients. This webpage shall also provide references to the lists of actual shortages published by the competent authorities of the Member State pursuant to Article 121(1), point (b).

Article 125

*Obligations on the marketing authorisation holder in case of a critical shortage **of Union concern***

1. Following the addition of a medicinal product to the list of critical shortages **of Union concern** of medicinal products in accordance with Article 123, paragraphs 1 and 2, or recommendations provided in accordance with Article 123(4), the marketing authorisation holder ~~as defined in Article 116(1)~~ and subject to those recommendations shall:
   (a) provide any additional information that the Agency may request;
   (b) provide additional relevant information to the Agency;
   (c) take into account the recommendations referred to in Article 123(4);
   (d) **take into account the actions taken by the Commission pursuant to Article 126 (1)** ~~comply with any measures taken by the Commission pursuant to Article 126(1), point (a), or actions taken by the Member State pursuant to Article 121(5), point (d)~~;
   (e) inform the Agency of any measures taken pursuant to points (c) and (d) and the report on results of such measures;
   (f) inform the Agency **and the competent authority of the Member State** of the end date of the critical shortage **of Union concern**.

Article 126

Role of the Commission

1. The Commission**:** ~~shall, where it considers it appropriate and necessary:~~
   (a) **shall** take into account the MSSG recommendations ~~and implement relevant measures~~;
   (aa) shall take any ~~necessary~~ actions, within the limits of the powers conferred on the Commission, to address critical shortages of Union concern where it considers it appropriate and necessary;
   (b) **shall** inform the MSSG of those **actions** ~~measures~~ taken **pursuant to letter (aa) ~~where it considers it appropriate and necessary~~.** ~~by the Commission.~~

2. The Commission may request the MSSG to provide recommendations referred to in Article 123(4).

2a. ~~When justified for public health reasons, the Commission is empowered to adopt, taking into consideration the MSSG recommendations, referred to in Article 123, paragraph 4a, delegated acts in accordance with Article 175 to supplement this Regulation to require marketing authorisation holders to have and keep up to date a shortage prevention plan in accordance with Article 117, paragraph 1, for medicinal products other than critical medicinal products identified by the competent authority of the Member State pursuant to Article 127, paragraph 1.~~

The Commission is empowered to adopt a delegated act supplementing this Regulation to identify additional medicinal products that require a shortage prevention plan, in accordance with the requirements set out in Article 117.

Those delegated acts shall be adopted taking due account of the likelihood of shortages and the actual risks to public health arising from shortages relating to such medicinal products. To this end, the following criteria shall guide the identification of these medicinal products:

(a) The number and frequency of past critical shortages reported to the MSSG;

(b) The specific characteristics of the medicinal products concerned including the existence of available alternative authorised medicinal products;

(c) The severity of the conditions intended to be treated;

(d) Other potential risks to public health.

When the Commission adopts a delegated act pursuant to this paragrah, it shall take into account MSSG recommendations adopted in accordance with Article 123 (4a).

SECTION 2
SECURITY OF SUPPLY

Article 127
Identification and management of critical medicinal products by the competent authority of the Member State

1. ~~**For the purposes of establishing the Union list of critical medicinal products referred to in Article 131 (1),**~~ T~~t~~he competent authority of the Member State shall identify ~~critical~~ medicinal products in that Member State~~, using~~ **using** the methodology set out in Article 130(1), point (a). ~~**The Member State shall make public a list of the critical medicinal products identified pursuant to this subparagraph.**~~

~~**In addition to the first subparagraph, the Member State may establish a national list of critical medicinal products using a national methodology or the methodology set out in Article 130 (1), point (a).**~~

The Commission shall adopt and update the list of critical medicinal products identified by the competent authorities of the Member States according to paragraph 1 by means of an implementing act and communicate the adoption of the list and any updates to the Agency and the MSSG. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

2. The competent authority of the Member State acting through the working party referred to in Article 121(1), point (c), shall report to the Agency the critical medicinal products in that Member State **identified** ~~identified~~ pursuant to the paragraph 1, **first subparagraph,** as well as the information received from the marketing authorisation holder ~~as defined in Article 116(1)~~.

3. ~~For the purposes of the identification of critical medicinal products referred to in paragraph 1, the competent authority of the Member State may request relevant information including the shortage prevention plan referred to in Article 117 from the marketing authorisation holder as defined in Article 116(1).~~ **For the purposes of the identification of critical medicinal products referred to in paragraph 1, first subparagraph, using the methodology pursuant to Article 130(1), point a, the competent authority of the Member State may request relevant information from the marketing authorisation holder.**

4. For the purposes of the **identification of critical medicinal products referred to in paragraph 1, using the methodology pursuant to Article 130(1), point a**~~, first subparagraph~~ ~~identification~~ of ~~critical medicinal products referred to in paragraph 1~~, the competent authority of the Member State may request relevant information from other entities including other marketing authorisation holders, importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public.

5. The competent authority of the Member State shall assess the merits of each confidentiality claim made by the marketing authorisation holder pursuant to Article 128(1), point (e), and shall protect any information that is commercially confidential against unjustified disclosure.

6. For the purposes of the adoption of the Union list of critical medicinal products pursuant to Article 131, each Member State shall, through the competent authority of the Member State concerned:

(a) submit to the Agency the information referred to in Article 130(2), point (a), using the tools, methods of and criteria for the monitoring and reporting established pursuant to Article 130(1), point (c), by the deadline set by the Agency;
(b) provide any relevant information to the Agency, including information on measures that have been taken by the Member State to strengthen the supply of that medicinal product;
(c) provide updates to the information provided in accordance with points (a) and (b) to the Agency where necessary;
(d) justify any failure to provide any of the requested information;
(e) indicate the existence of any commercially confidential information reported as such by the marketing authorisation holder pursuant to Article 128(1), point (e), and provide the marketing authorisation holder's explanation of why that information is of a commercially confidential nature.

Where necessary, the competent authority of the Member State may request an extension of the deadline set by the Agency to comply with the request for information in accordance with point (a) of the first subparagraph.

7. Following the addition of a medicinal product to the Union list of critical medicinal products in accordance with Article 131 or any recommendations provided in accordance with Article 132(1), the Member States shall:
(a) provide any additional information that the Agency may request;
(b) provide additional relevant information to the Agency;
(c) ~~comply and~~ coordinate with any **actions** ~~measures~~ taken by the Commission pursuant to Article 134(1), point (a**a**);
(d) take into account any MSSG recommendations referred to in Article 132(1);
(e) inform the Agency of any actions foreseen or taken in accordance with point (c) and (d) by that Member State, as well as the results of these actions.

8. Member States that take an alternative course of action in respect of paragraph 7, points (c) and (d), shall share the reasons for doing so with the Agency in a timely manner.

Article 2

Definitions

(13) 'critical medicinal product' means a medicinal product for which insufficient supply results in serious harm or risk of serious harm to patients~~, and identified using the methodology pursuant to Article 130(1), point (a).~~

Article 128

Obligations of the marketing authorisation holder with regard to critical medicinal products

1. For the purposes of Article 127, paragraphs 1 and 3, and Article 131(1), the marketing authorisation holder ~~as defined in Article 116(1)~~ shall:
   (a) submit the information requested in accordance with Articles 127(3), 130(2), point (b), and 130(4), point (b), to the competent authority concerned ~~as defined in Article 116(1)~~, without undue delay, using the tools, methods of and criteria for the monitoring and reporting established pursuant to Article 130(1), point (c), by the deadline set by that competent authority concerned;
   (b) provide updates to the information provided in accordance with point (a) where necessary;
   (c) justify any failure to provide any of the requested information;
   (d) where necessary, submit a request to the competent authority concerned ~~as defined in Article 116(1)~~ for an extension of the deadline set by that competent authority in accordance with point (a), and
   (e) indicate whether the information provided in accordance with point (a) contain any commercially confidential information, identify the relevant parts of that information having a commercially confidential nature and explain why that information is of such nature.

2. The marketing authorisation ~~as defined in Article 116(1)~~ authorisation shall be responsible for providing correct, not misleading, and complete information as requested by the competent authority concerned ~~as defined in Article 116(1)~~ and shall have the duty to cooperate and to disclose on their own motion any relevant information without undue delay to that competent authority and to update the information as soon as that information becomes available.

Article 129

Obligations on other actors

For the purposes of Article 127(4) and Article 130(2), point (c), and Article 130(4), point (c), where relevant, upon request from the competent authority concerned as defined in Article 116(1), entities including other marketing authorisation holders as defined in Article 116(1), importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public shall provide any information ~~requested in a timely manner.~~ **within the timeframe specified by the competent authority concerned.**

Article 130

Role of the Agency

1. The Agency shall, in collaboration with the working party referred to in Article 121(1), point (c), ensure the following:
   (a) develop a common methodology to identify critical medicinal products, including the evaluation of vulnerabilities with respect to the supply chain of those medicines, in consultation, where appropriate, with relevant stakeholders;
   (b) specify the procedures and criteria for establishing and reviewing the Union list of critical medicinal products referred to in Article 131;
   (c) specify the tools, methods of and criteria for the monitoring and reporting provided for in Articles 127(6), point (a), and 128(1), point (a);
   (d) specify the methods for the provision and review of MSSG recommendations referred to in Article 132, paragraphs 1 and 3.

   The Agency shall publish the information referred to in points (b), (c) and (d) on a dedicated webpage on its web-portal.

2. Following the reports and information provided by the Member States and marketing authorisation holders in accordance with Article 127, paragraphs 2 and 6, and Article 128(1), the Agency, may request the relevant information from:

(a) the competent authority of the Member State concerned;
(b) the marketing authorisation holder of the medicinal product, including the shortage prevention plan, referred to in Article 117;
(c) other entities including other marketing authorisation holders, importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public.

The Agency, in consultation with the working party referred to in Article 121(1), ~~-~~point (c), shall report the information referred to in Article 127, paragraphs 2 and 6, and Article 128(1) to the MSSG.

3. For the purposes of Article 127(6), point (e), and Article 128(1), point (e), the Agency shall assess the merits of each confidentiality claim and protect commercially confidential information against unjustified disclosure.
4. Following the adoption of the Union list of critical medicinal products ~~in accordance with Article 131,~~ the Agency may request additional information from:
   (a) the competent authority of the Member State concerned;
   (b) the marketing authorisation holder ~~as defined in Article 116(1)~~;
   (c) other entities including other marketing authorisation holders, importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public.

5. Following the adoption of the Union list of critical medicinal products in accordance with Article 131, the Agency shall report to the MSSG on any relevant information received from the marketing authorisation holder pursuant to Article 133 and the competent authority of the Member State in accordance with Article 127, paragraphs 7 and 8.

6. The Agency shall make publicly available via the web-portal referred to in Article 104 the MSSG recommendations referred to in Article 132(1).

Article 131

The Union List of Critical Medicinal Products

1. Following the reporting referred to in Article 130, paragraph 2, second subparagraph, and Article 130(5), the MSSG shall consult the working party referred to in Article 121(1), point (c). Based on this consultation, the MSSG shall propose a Union list of critical medicinal products authorised to be placed on the market of a Member State pursuant to Article 5 of [revised Directive 2001/83/EC] and for which **the** coordinated Union level action **foreseen in this chapter** is necessary ("the Union list of critical medicinal products").

2. The MSSG may propose updates to the Union list of critical medicin**ales** ~~es~~ **products** to the Commission, where necessary.

The first revision and possible update shall take place no later than one year after the date of entry into application of this Regulation.

3. The Commission, taking into account the proposal of the MSSG, shall adopt and update the Union list of critical medicinal products by means of an implementing act and communicate the adoption of the list and any updates to the Agency and the MSSG. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

4. Following the adoption of the Union list of critical medicinal products in accordance with paragraph 3, the Agency shall immediately publish this list and any updates to this list on its web-portal referred to in Article 104.

Article 132

Role of the MSSG

1. Following the adoption of the Union list of critical medicinal products pursuant to Article 131(3), in consultation with the Agency and the working party referred to in Article 121(1), point (c), the MSSG may provide recommendations, in accordance with the methods referred to in Article 130(1), point (d), on appropriate security of supply measures to marketing authorisation holders ~~as defined in Article 116(1)~~, the Member States, the Commission**, the Agency** or other entities. Such measures may include**, inter alia,** recommendations on diversification of suppliers**,** ~~and~~ inventory management **and regulatory flexibilities**.

2. The MSSG shall amend its rules of procedure, and the rules of procedure of the working party referred to in Article 121(1), point (c), in accordance with the tasks set out in this section.

3. Following the report pursuant to Article 130(5), the MSSG shall review its recommendations in accordance with the methods referred to in Article 130(1), point (d).

4. The MSSG may request the Agency to request further information from the Member States or marketing authorisation holder of the medicinal product ~~as defined in Article 116(1)~~ and included on the Union list of critical medicinal products or other relevant entities referred to in Article 129.

Article 133

Obligations on the marketing authorisation holder after the MSSG recommendations

Following the addition of a medicinal product to the Union list of critical medicinal products in accordance with Article 131(3) or **following** any recommendations provided in accordance with Article 132(1), the marketing authorisation holder ~~as defined in Article 116(1)~~ of a medicinal product on that list or subject to those recommendations shall:

(a) provide any additional information that the Agency may request;

(b) provide additional relevant information to the Agency;

(c) take into account the recommendations referred to in Article 132(1);

(d) ~~comply with~~ **take into account the** ~~any measures~~ **actions** taken by the Commission in accordance with Article 134(1)**;** ~~, point (a), or by the Member State pursuant to Article 127(7), point (e);~~

(e) inform the Agency of any measures taken and report on the results of such measures.

Article 134

Role of the Commission

1. The Commission ~~may, where it considers it appropriate and necessary~~:

   (a) **shall** take into account the MSSG recommendations ~~and implement the relevant measures;~~

   (aa) shall ~~**may**~~ **take, if appropriate, any necessary** ~~**relevant**~~ ~~**non-binding**~~ **actions within the limits of the powers conferred on the Commission, including the development of guidelines to improve the security of supply;**

   (ab) may foster coordination of Member State measures aimed at ensuring security of supply within their territories.

   (b) **shall** inform the MSSG of those ~~measures~~ **actions** taken by the Commission.

   (c) **may** request the MSSG to provide information or an opinion or further recommendations referred to in Article 132(1).

2. **If necessary to ensure the smooth functioning of the internal market ,** ~~The~~ **the** Commission **is empowered to adopt**, taking into consideration the **recommendations** ~~information or the opinion,~~ referred to in paragraph 1, ~~or MSSG recommendations,~~ ~~may decide to~~ ~~adopt~~ an implementing act to **provide for uniform** ~~**application and**~~ **temporary criteria** ~~**for national measures aiming at**~~ **to improve** ~~**ing**~~ **the security of supply of medicinal products included in the Union list of critical medicinal products or a decision to set uniform and specific requirements, in particular regarding contingency stocks.**

   The criteria shall apply in all Member States when they adopt measures to improve security of supply. The criteria shall be aimed at preventing or mitigating fragmentation in the internal market, while pursuing a high level of human health protection.

The adoption of these criteria shall be limited to cases where the Commission identifies a highly likely disruption of the internal market which negatively affects the security of supply of critical medicinal products. They shall take into account:

(a) the severity of the disruption of the internal market, or the risk thereof;

(b) the causes of the disruption to security of supply and the actual or potential emergence of national rules to resolve it;

(c) the existence of other available measures under this Regulation to mitigate or resolve the disruption;

(d) the gravity and scope of risks to public health.

The criteria shall be based on objective, factual, measurable and substantiated data, including from the Agency and its preparatory bodies, national competent authorities and relevant economic operators. The criteria shall be proportionate, non-discriminatory and comply with competition rules.

The Commission shall clearly define the temporary scope of these criteria.

Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

~~**or to impose Union level contingency stock requirements of active pharmaceutical ingredients or finished dosage forms or other relevant measures required to improve security of supply on marketing authorisation holders, wholesale distributors or other relevant entities. improve security of supply within the Union, with a view to ensure the good functioning of the internal market. These measures shall be limited to cases where the Commission identifies a likely disruption of the internal market due to severe risk of disruption of the security of supply within the Union that cannot be resolved through existing instruments or actions and that is liable to affect the security of supply of medicinal products on the Union list of critical medicinal products. For nationally authorised products, these measures shall be addressed at Member States.** improve security of supply. The implementing act may impose contingency stock requirements of active pharmaceutical ingredient or finished dosage forms, or other relevant measures required to improve security of supply, on marketing authorisation holders, wholesale distributors or other relevant entities.~~

~~**The implementing act shall be limited to measures aimed at ensuring appropriate stock levels, such as requirements of contingency stocks, and ensuring approriate supplies of medicinal products to wholesale distributors, pharmacies or persons authorised to supply medicinal products. These measures shall be proportionate and necessary to the objective pursued, with due regard to the protection of fundamental rights.**~~

~~2a.~~ The implementing powers referred to in paragraph 2 and 2a of this Article shall not affect measures adopted by the Member States, the Council or the Commission pursuant to [EMA revised mandate, HERA Regulation, CBHT] concerning supply of critical countermeasures during a major event or a public health emergency at Union level.

3. The implementing act referred to in paragraph 2 shall be adopted in accordance with the examination procedure referred to in Article 173(2).

CHAPTER XII
GENERAL PROVISIONS

Article 171
Penalties at national level

1. Member States shall lay down the rules on penalties applicable to infringements of this Regulation 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.

2. Member States shall inform the Commission immediately of any litigation instituted for infringement of this Regulation **regarding centrally authorised medicinal products**.

Article 172

Union penalties

1. The Commission may impose financial penalties in the form of fines or periodic penalty payments on the marketing authorisations holder granted under this Regulation if they fail to comply with any of the obligations laid down in Annex II in connection with the marketing authorisations.

2. The Commission may, insofar as specifically provided for in the delegated acts referred to in paragraph 10, point (b), impose the financial penalties referred to in paragraph 1 on a legal entity or legal entities other than the marketing authorisation holder provided that such entities form part of the same economic entity as the marketing authorisation holder and that such other legal entities:
   (a) exerted a decisive influence over the marketing authorisation holder; or
   (b) were involved in, or could have addressed, such failure to comply with the obligation by the marketing authorisation holder.

3. Where the Agency or a competent authority of a Member State is of the opinion that a marketing authorisation holder has failed to comply with any of the obligations, referred to in paragraph 1, it may request the Commission to investigate whether to impose financial penalties pursuant to that paragraph.

4. In determining whether to impose a financial penalty and in determining its appropriate amount, the Commission shall be guided by the principles of effectiveness, proportionality and dissuasiveness and take into consideration, where relevant, the seriousness and the effects of the failure to comply with the obligations.

5. For the purposes of paragraph 1, the Commission shall take into account:
   (a) any infringement procedure initiated by a Member State against the same marketing authorisation holder on the basis of the same legal grounds and the same facts;
   (b) any sanctions, including penalties, already imposed on the same marketing authorisation holder on the basis of the same legal grounds and the same facts.

6. Where the Commission finds that the marketing authorisation holder has failed, intentionally or negligently, to comply with its obligations, as referred to in paragraph 1, it may adopt a decision imposing a fine not exceeding 5 % of the marketing authorisation holder's Union turnover in the business year preceding the date of that decision.

   Where the marketing authorisation holder continues to fail to comply with its obligations referred to in paragraph 1, the Commission may adopt a decision imposing periodic penalty payments per day not exceeding 2,5 % of the marketing authorisation holder's average daily Union turnover in the business year preceding the date of that decision.

   Periodic penalty payments may be imposed for a period running from the date of notification of the relevant Commission's decision until the failure to comply with the obligation by the marketing authorisation holder, as referred to in paragraph 1, has been brought to an end.

7. When conducting the investigation on a failure to comply with any of the obligations referred to in paragraph 1, the Commission may cooperate with competent authorities of the Member States and rely on resources provided by the Agency.

8. Where the Commission adopts a decision imposing a financial penalty, it shall publish a concise summary of the case, including the names of the marketing authorisation holders involved and the amounts of and reasons for the financial penalties imposed, having regard to the legitimate interest of the marketing authorisation holders for the protection of their business secrets.

9. The Court of Justice of the European Union shall have unlimited jurisdiction to review decisions whereby the Commission has imposed financial penalties. The Court of Justice of the European Union may cancel, reduce or increase the fine or periodic penalty payment imposed by the Commission.

10. The Commission is empowered to adopt delegated acts in accordance with Article 175 in order to supplement this Regulation by laying down:
    (a) procedures to be applied by the Commission when imposing fines or periodic penalty payments, including rules on the initiation of the procedure, measures of inquiry, rights of the defence, access to file, legal representation and confidentiality;
    (b) further detailed rules on the imposition by the Commission of financial penalties on legal entities other than the marketing authorisation holder;
    (c) rules on duration of procedure and limitation periods;
    (d) elements to be taken into account by the Commission when setting the level of and imposing fines and periodic penalty payments, as well as the conditions and methods for their collection.

ANNEX II

LIST OF THE OBLIGATIONS REFERRED TO IN ARTICLE 172

(1) the obligation to submit complete and accurate particulars and documentation in an application for marketing authorisation submitted to the Agency or in response to obligations laid down in this Regulation to the extent that the failure to comply with the obligation concerns a material particular;

(2) the obligation to comply with conditions or restrictions included in the marketing authorisation and concerning the supply or use of the medicinal product for human use, as referred to in Article 12 (4), point (c) and in Article 13(1) fourth subparagraph;

(3) the obligation to comply with conditions or restrictions included in the marketing authorisation with regard to the safe and effective use of the medicinal product for human use as referred to in Article 12(4), points (b), (d), (e), (f) and (g) and in Article 13(1);

(4) the obligation to introduce any necessary variation to the terms of the marketing authorisation to take account of technical and scientific progress and enable the medicinal products for human use to be manufactured and checked by means of generally accepted scientific methods, as provided for in Article 45(1);

(5) the obligation to supply any new information which may entail a variation to the terms of the marketing authorisation, to notify any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product for human use is marketed, or to supply any information that may influence the evaluation of the risks and benefits of the product, as provided for in Article 45(2);

(6) the obligation to keep product information up to date with current scientific knowledge, including the conclusions of the assessment and recommendations made public on the European medicines web-portal, as provided for in Article 45(3);

(7) the obligation to provide, at the request of the Agency, any data demonstrating that the benefit-risk balance remains favourable, as provided for in Article 45(4);

(8) the obligation to place the medicinal product for human use on the market in accordance with the content of the summary of product characteristics and the labelling and package leaflet as contained in the marketing authorisation;

(9) the obligation to comply with the conditions referred to in Article 18(1) and Article 19;

(10) the obligation to notify the Agency of the dates of actual marketing and of the date when the medicinal product for human use ceases to be on the market, and to provide to the Agency data relating to the volume of sales and the volume of prescriptions of the medicinal product for human use, as provided in Article 16(4);

(11) the obligation to operate a comprehensive pharmacovigilance system for the fulfilment of pharmacovigilance tasks, including the operation of a quality system, maintenance of a pharmacovigilance system master file and performance of regular audits, in accordance with Article 99 in conjunction with Article 99 of [revised Directive 2001/83/EC];

(12) the obligation to submit, at the request of the Agency, a copy of the pharmacovigilance system master file, as provided for in Article 45(4);

(13) the obligation to operate a risk management system as provided for in Article 22 and Article 99(2) in conjunction with Article 99(4) of [revised Directive 2001/83/EC];

(14) the obligation to record and report suspected adverse reactions for medicinal products for human use, in accordance with Article 106 (1) in conjunction with Article 105 of [revised Directive 2001/83/EC];

(15) the obligation to submit periodic safety update reports, in accordance with Article 106(2) in conjunction with of [revised Directive 2001/83/EC];

(16) the obligation to conduct post-marketing studies, including post-authorisation safety studies and post-authorisation efficacy studies, and to submit them for review, as provided for in Article 20;

(17) the obligation to ensure that public announcements relating to information on pharmacovigilance concerns are presented objectively and are not misleading and to notify them to the Agency, as provided for in Articles 104 of [revised Directive 2001/83/EC];

(18) the obligation to comply with the time limits for initiating or completing measures specified in the Agency's decision on deferral following the initial marketing authorisation of the medicinal product for human use concerned and in accordance with the definitive opinion referred to in Article 81(2);

(19) the obligation to submit to the Agency an updated version of the paediatric investigation plan in accordance with the agreed timing as provided for in Article 74(2) and Article 74(3);

(20) the obligation to place the medicinal product for human use on the market within two years of the date on which the paediatric indication is authorised, as provided for in Article 59 of [revised Directive 2001/83/EC];

(21) the obligation to notify the Agency the intention to discontinue the placing on the market of the product no less than six months before the discontinuation as provided for in Article 60 of [revised Directive 2001/83/EC];

(22) the obligation to transfer the marketing authorisation or to allow a third party to use documentation contained in the file of the medicinal product, as provided for in Article 60 of [revised Directive 2001/83/EC];

(23) the obligation to notify the Agency of the intention to discontinue the conduct of an agreed paediatric investigation plan and provide the reasons for such discontinuation no less than six months before the discontinuation as provided in Article 88;

(24) the obligation to submit paediatric studies to the Agency or to the Member States, including the obligation to enter information on third country clinical trials into the European database, as provided for in Articles 91;

(25) the obligation to submit to the Agency a paediatric investigation plan with a request for agreement or an application for a waiver from it, not later than upon completion of the human pharmaco-kinetic studies in adults, except in duly justified cases, as provided for in Article 76(1)~~.~~**;**

(26) the obligation to notify in accordance with ~~a~~Article 116, paragraph 1, points (a), (b), (c) and (d) ~~a decision to permanently cease or temporarily suspend the marketing of a medicinal product, or permanently withdraw the marketing authorisation for that medicinal product~~.

REVISED DIRECTIVE

Chapter V

Obligations and liability of the marketing authorisation holder

Article 56

General obligations

3. The marketing authorisation holder of a medicinal product placed on the market in a Member State shall, within the limits of its responsibility, ensure appropriate **stock levels** and continued supplies of that medicinal product to wholesale distributors, pharmacies or persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered.

The arrangements for implementing the first subparagraph should, moreover, be justified on grounds of public health protection and be proportionate in relation to the objective of such protection, in compliance with the Treaty rules, particularly those concerning the free movement of goods and competition.

Chapter XII
Wholesale distribution and sale at a distance

Article 162
Wholesale distribution of medicinal products

3. Distributors who intend to import a medicinal product from another Member State shall notify the marketing authorisation holder and the competent authority of the Member State to which the medicinal product is to be imported of their intention to import that medicinal product.

4. In the case of medicinal products covered by a national marketing authorisation, the notification referred to in paragraph 3 to the competent authority of the Member State shall be without prejudice to additional procedures provided for in the legislation of that Member State and to fees payable to the competent authority of the Member State for examining the notification.

5. In the case of medicinal products covered by a centralised marketing authorisation, the 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

Obligations of the wholesale distribution authorisation holder

1. Member States shall ensure that wholesale distribution authorisation holders shall:
   (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 official representatives of the competent authority of the Member State access to their premises, installations and equipment referred to in Article 164(2), point (a), at all times;
   (c) obtain, 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 163(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 67(2), second subparagraph;
   (f) have an emergency plan that ensures effective implementation of any recall from the market ordered by the competent authorities or carried out in cooperation with the manufacturer or 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 67;
   (h) keep the records referred to in point (g) available to the competent authorities of the Member States, for inspection purposes, for a period of five years;

(i) comply with the principles of good distribution practices for medicinal products laid down in Article 160;

(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 an adequate 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, which shall be defined in the national legislation;

(m) cooperate with marketing authorisation holders and competent authorities of the Member States on the security of supply.

Article 167

Obligation of supply of medicinal products

1. With regard to the supply of medicinal products to pharmacists and persons authorised or entitled to supply medicinal products to the public, Member States shall not impose upon the wholesale distribution authorisation holder 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 pharmacies and persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered.

3. The arrangements for implementing this Article should, moreover, be justified on grounds of public health protection and be proportionate in relation to the objective of such protection, in compliance with the Treaty rules, particularly those concerning the free movement of goods and competition.

Chapter XVI
General provisions

Article 203

Information on prohibition of supply or other action on a marketing authorisation

1. Each Member State shall take all the appropriate measures to ensure that decisions granting marketing authorisation, refusing or revoking a marketing authorisation, cancelling 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. ~~In addition to the notification made pursuant to Article 116 of [revised Regulation (EC) No 726/2004], the marketing authorisation holder shall declare without undue delay if such notified action is based on any of the grounds set out in Articles 195 or 196(1).~~

The marketing authorisation holder shall notify the national competent authority without undue delay of any action they take 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 if such notified action is based on any of the grounds set out in Articles 195 or 196(1) and specify the grounds for such action.

2a. ~~**If a marketing authorisation holder submits a notification pursuant to Article 116(1) of [revised Regulation (EC) No 726/2004], it shall concomitantly notify, without undule delay, in accordance with paragraph 2 [where that notification is also based on any of the grounds listed in paragraph 2].**~~

The marketing authorisation holder shall make the notification electronically and in the formats made available by the Agency. **The Agency shall consult the Member States when drawing up the formats.**

3. The marketing authorisation holder shall also make the notification pursuant to paragraph 2 in cases where the action is taken in a third country **and where such action is based on any of the grounds set out Articles 195 or 196(1).** ~~and where such action is based on any of the grounds set out Articles 195 or 196(1)~~.

4. The marketing authorisation holder shall furthermore notify the Agency where the action referred to in paragraphs 2 or 3 is based on any of the grounds referred to in Articles 195 or 196(1).

5. The Agency shall forward notifications received in accordance with paragraph 4 to all Member States without undue delay.

6. Member States shall ensure that appropriate information about action taken pursuant to paragraphs 1 and 2 that may affect the protection of public health in third countries is without undue delay brought to the attention of the World Health Organization, with a copy to the Agency.

7. 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, whose supply has been prohibited or that have been withdrawn from the market, including the reasons for such action.

5TH READING PACKAGE

GOVERNANCE OF EMA

RECITALS

PROPOSED REGULATION

(12) The structure and operation of the various bodies making up the Agency should be designed in such a way as to take into account the need to constantly renew scientific expertise, the need for cooperation between Union and national bodies, the need for adequate involvement of civil society, and the future enlargement of the Union. The various bodies of the Agency should establish and develop appropriate contacts with the parties concerned, in particular with representatives of patients and healthcare professionals.

(13) The chief task of the Agency should be to provide Union institutions and Member States with the best possible scientific opinions to enable them to exercise the powers of authorisation and supervision of medicinal products conferred on them by Union legal acts in the field of medicinal products. Marketing authorisation should be granted by the Commission only after a single scientific evaluation procedure addressing the quality, safety and efficacy of high-technology medicinal products has been conducted by the Agency, applying the highest possible standards.

(14) To ensure close cooperation between the Agency and scientists operating in Member States, the composition of the Management Board should be such as to guarantee that the competent authorities of the Member States are closely involved in the overall management of the Union system for authorising medicinal products.

(15) The Agency's budget should be composed of fees and charges paid by the private sector and contributions from the Union budget to implement Union policies and contributions paid from third countries.

(16) Exclusive responsibility for preparing the Agency's opinions on all questions concerning medicinal products for human use should be vested in the Committee for Medicinal Products for Human Use.

(17) The creation of the Agency through Council Regulation (EEC) No 2309/937 which was replaced by Regulation (EC) No 726/2004 has made it possible to reinforce the scientific evaluation and monitoring of medicinal products in the Union, in particular through its scientific bodies and committees for which competent authorities of the Member States provide experts and expertise, ensuring a high quality and independent assessment. This Regulation does not establish a new Agency. The Agency mentioned in this Regulation is the Agency established by Regulation (EC) No 726/2004.

(18) The field of activity of the scientific committees should be enlarged and their operating methods and composition modernised. In this regard it is important to ensure patient and healthcare professional representation in the Committee for Human Medicinal Products as it is the main evaluation committee of the Agency for medicinal products for human use.

(19) Scientific advice for future applicants seeking a marketing authorisation should be provided more generally and in greater depth. Similarly, structures allowing the development of advice for companies, in particular small and medium-sized enterprises ('SMEs'), should be put in place.

(20) Promising medicinal products that have the potential to significantly address patients' unmet medical needs should benefit from early and enhanced scientific support. Such support will ultimately help patients benefit from new therapies as early as possible.

(21) In order to allow for advice that is more informative and an exchange of information between different bodies, scientific advice provided by the Agency should sometimes take place in parallel to scientific advice provided by other bodies. This should be the case for the joint scientific consultation carried out by the Member State Coordination Group on Health Technology Assessment foreseen in Regulation (EU) 2021/2282 of the European Parliament and of the Council8 and, in cases of medicinal products involving a medical device, the consultation of the expert panels as described in Article 106 of Regulation (EU) No 2017/745 of the European Parliament and of the Council9. Where parallel scientific advice consultation mechanisms are established under other relevant Union legal acts, a similar mechanism should apply.

(22) It is also necessary to reinforce the role of the scientific committees in such a way as to enable the Agency to participate actively in international scientific dialogue and to develop certain activities that will be necessary, in particular regarding international scientific harmonisation and technical cooperation with the World Health Organization.

(23) Furthermore, without prejudice to the provisions laid down in Regulation (EU) 2019/6, which remain applicable for veterinary medicinal products, in order to create greater legal certainty, it is necessary to define the responsibilities regarding the transparency rules for the Agency's work, to set certain conditions for the marketing of medicinal products authorised by the Union, to confer on the Agency powers to monitor the distribution of medicinal products authorised by the Union, to carry out inspections together with the Member States in third countries, and to specify the sanctions and the procedures for implementing them in the event of failure to observe the provisions of this Regulation and the conditions contained in the marketing authorisations granted under the procedures it establishes.

(24) In particular, the Agency should be empowered and given the capacity to carry out inspections, where this is in the interest of the Union and where the competent authorities of the Member States request support in carrying out their tasks under revised Directive 2001/83/EC of the European Parliament and of the Council10. The interest of the Union may concern situations where, to ensure faster access to medicinal products, challenges with inspections capacities at national level have to be addressed in a timely manner or where a response to a public health emergency or a major event requires immediate action. Providing the Agency with appropriate inspection capacity will also, in the interest of the Union, facilitate the dissemination of best practices, know-how, and improve the oversight of manufacturing of medicinal products worldwide. Following the request from a competent authority of the Member State, the Agency, at its own discretion, can accept to either provide support to the inspections of sites located in the Union or to carry out inspections of sites located in third countries.

(25) In certain cases, shortcomings in Member States' system of supervision and related enforcement activities could risk to substantially hinder the achievement of the objectives of this Regulation and those of revised Directive 2001/83/EC which could even lead to the emergence of risks to public health. To address these challenges, harmonised inspection standards should be ensured through the establishment of a joint audit programme within the Agency. This joint audit programme will also further harmonise the interpretation of good manufacturing and distribution practices on the basis of Union legislative requirements. Moreover, it will support further mutual recognition of inspection outcomes between Member States and with strategic partners. Within the joint audit programme, the competent authorities are subject to regular audits conducted by other Member States to maintain an equivalent and harmonised quality system and to ensure an appropriate implementation of relevant good manufacturing and distribution practices into national laws and equivalence with other EEA inspectorates.

(26) An inspection working group, which provides input and recommendations on all matters relating, directly or indirectly, to **good clinical practice,** good manufacturing practice**,** ~~and~~ good distribution practice **and pharmacovigilance,** irrespective of the marketing authorisation procedure through different reporting lines, should be established within the Agency. In particular, that working group should be responsible for the establishment, development and overall supervision of the joint audit programme.

(27) To promote innovation and the development of new medicinal products by SMEs within the meaning of Commission Recommendation 2003/361/EC11, and to reduce the cost of the placing on the market of medicinal products for human use authorisedvia the centralised procedure, these undertakings should benefit from a support scheme from the Agency.

(28) The support scheme should be composed of regulatory, procedural and administrative support, and of a reduction, deferral or waiver of fees. The scheme should cover the various steps involved in pre-authorisation procedures, such as scientific advice, the submission of the marketing authorisation application, and post-authorisation procedures.

(29) Legal entities that are not engaged in an economic activity such as universities, public bodies, research centres or not-for-profit organisations, represent an important source of innovation and should also benefit from this support scheme. Whereas it should be possible to take account of the particular situation of these entities on an individual basis, such support can best be achieved by means of a dedicated support scheme, including administrative support and through the reduction, deferral and waiver of fees.

(30) The Agency should be empowered to give scientific recommendations on whether a product under development, which could potentially fall under the mandatory scope of the centralised procedure, meets the scientific criteria to be a medicinal product. Such an advisory mechanism would address, as early as possible, questions related to borderline cases with other areas such as substances of human origin, cosmetics or medical devices, which may arise as science develops. To ensure that recommendations given by the Agency take into account the views of equivalent advisory mechanisms in other legal frameworks, the Agency should consult the relevant advisory or regulatory bodies.

(31) To increase transparency of scientific assessments and all other activities, a European medicines web-portal should be created and maintained by the Agency.

(32) Experience with the functioning of the regulatory system has shown that the existing European Medicines Agency multi-scientific committee structure often creates complexity in the scientific assessment process among committees, duplication of work and non-optimised use of expertise and resources. In addition, the Agency and the competent authorities of the Member States are confronted with challenges related to limited capacity and appropriate expertise to deal with increasing number of procedures related to existing medicinal products and assessment of new ones, in particular cutting edge innovative and complex medicinal products.

(33) To optimise the functioning and efficiency of the regulatory system, the structure of the Agency's scientific committees is simplified and reduced to two main Committees for medicinal products for human use, the Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC).

(34) The simplification of procedures should not have an impact on standards or the quality of scientific evaluation of the medicinal products to guarantee the quality, safety and efficacy of medicinal products. ~~It should also allow for the reduction of the scientific evaluation period from 210 days to 180 days.~~

(35) The Agency's scientific committees should be able to delegate some of their evaluation duties to working parties which should be open to experts from the scientific world and appointed for this purpose, whilst retaining complete responsibility for the scientific opinions issued by them.

(36) The expertise of the Committee for Advanced Therapies (CAT), the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO) andCommittee for Herbal Medicinal Products (HMPC) is retained through working groups, working parties and a pool of experts who are organised based on different domains and who are giving input to the CHMP and PRAC. The CHMP and PRAC consists of experts from all Member States while working parties consist in majority of experts appointed by the Member States, based on their expertise, and of external experts. The model of rapporteurs remains unchanged. **The efficiency gain, involvement of adequate scientific expertise and broad geographic representation of experts in the scientific committees, working parties and working groups will be ensured as part of the strategy for the organizational management and internal control systems** adopt a strategy for the organisational management and internal control systems.Representation of patients and health care professionals, with expertise in all areas, including rare and paediatric diseases, is increased at the CHMP and PRAC, in addition to the dedicated working groups representing patients and health care professionals.

(37) Scientific committees like the CAT have been instrumental to ensure expertise and capacity building in an emerging technological field. However, after more than 15 years, advanced therapy medicinal products are now more common. The full integration of their assessment in the work of the CHMP will facilitate the assessment of medicinal products within the same therapeutic class, independent of the technology on which they are based. It will also ensure that all biological medicinal products are assessed by the same committee.

(38) To allow for more informative advice on clinical trial applications and therefore a more integrated development advice in view of future data requirements for marketing authorisation applications, the Agency can engage in consultation with representatives from Member States with clinical trial expertise. Nevertheless, decisions on clinical trial applications should remain within the competence of the Member States, in accordance with Regulation (EU) No 536/2014 of the European Parliament and of the Council12.

(39) To allow for a more informative decision making and for exchange of information and pooling of knowledge on general issues of scientific or technical nature related to the tasks of the Agency regarding medicinal products for human use, in particular to scientific guidelines on unmet medical needs and the design of clinical trials, or other studies and the generation of evidence along the life cycle of medicinal product, the Agency should be able to have recourse to a consultation process of authorities or bodies active along the life cycle of medicinal products. These authorities could be, as appropriate, representatives from Heads of Medicines Agencies, the Clinical Trial Coordination and Advisory Group, the SoHO Coordination Board, the Coordination Group on Health Technology Assessment, Medical Devices Coordination Group, medical devices national competent authorities, national competent authorities for pricing and reimbursement of medicines, national insurance funds or healthcare payers. The Agency should also be able to extend the consultation mechanism to consumers, patients, healthcare professionals, industry, associations representing payers, or other stakeholders, as relevant.

(40) Member States should ensure adequate funding of competent authorities to carry out their tasks under this Regulation and under [revised Directive 2001/83/EC]. In addition, in line with the Joint Statement of the European Parliament, the Council of the EU and the European Commission on decentralised agencies13, Member States should ensure adequate resources are assigned by the competent authorities of theMember 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.

(41) In the context of cooperation with international organisations to support global public health, it is important to leverage the scientific assessment performed by the Union and to promote reliance by third country regulatory authorities based on the use of certificates of medicinal products for authorised medicinal products in the Union. An applicant may request independently or as part of an application under the centralised procedure a scientific opinion from the Agency for the use of the medicinal product for markets outside the Union. The Agency should cooperate with the World Health Organization and relevant third country regulatory authorities and bodies to issue such scientific opinions.

(42) The Agency may cooperate with competent authorities of third countries in the context of performing its tasks. Such regulatory cooperation should be coherent with the broader economic relationship of the Union with the third country concerned, taking account of the relevant international agreements between the Union and that third country.

Chapter XI

European Medicines Agency

Section 1

Tasks of the Agency

Article 135

Establishment

The functioning of the European Medicines Agency established by Regulation (EC) No 726/2004 (the 'Agency') shall **be replaced and succeeded by the European Medicines Agency (the 'Agency') established by** ~~continue in accordance with~~ the present Regulation.

The Agency shall be responsible for coordinating the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products for human use and of veterinary medicinal products.

Article 136

Legal status

1. The Agency shall have legal personality.

2. In each of the Member States, the Agency shall enjoy the most extensive legal capacity accorded to legal persons under their laws. It may, in particular, acquire or dispose of movable and immovable property, and be party to legal proceedings.

3. The Agency shall be represented by an Executive Director.

Article 137

Seat

The seat of the Agency shall be established in Amsterdam, the Netherlands.

Article 138

Objectives and tasks of the Agency

1. The Agency shall provide the Member States and the institutions of the Union with the best possible scientific opinion on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human use, veterinary medicinal products, which is referred to it in accordance with the Union legal acts relating to medicinal products for human use or veterinary medicinal products.

   The Agency, acting particularly through its Committees, shall carry out the following tasks:

   (a) coordinating the scientific evaluation of the quality, safety and efficacy of medicinal products for human use, which are subject to Union marketing authorisation procedures;
   (b) coordinating the scientific evaluation of the quality, safety and efficacy of veterinary medicinal products, which are subject to Union marketing authorisation procedures in accordance with Regulation (EU) 2019/6 and the performance of other tasks set out in Regulation (EU) 2019/6 and Regulation (EC) 470/2009;
   (c) transmitting on request and making publicly available assessment reports, summaries of product characteristics, labels and package leaflets for the medicinal products for human use;

(ca) coordinating the assessment of the environmental risk assessments related to medicinal products for human use which are subject to Union marketing authorisation procedures in accordance with this Regulation or investigational medicinal products for human use containing or consisting of genetically modified organisms (GMOs);

(d) coordinating the monitoring of medicinal products for human use which have been authorised in the Union and providing advice on the measures necessary to ensure the safe and effective use of those products, in particular by coordinating the evaluation and implementation of pharmacovigilance obligations and systems and the monitoring of such implementation;

(e) ensuring the collation and dissemination of information on suspected adverse reactions to medicinal products for human use authorised in the Union by means of databases that are permanently accessible to all Member States;

(f) assisting Member States with the rapid communication of information on pharmacovigilance concerns relating to medicinal products for human use ~~to healthcare professionals~~ and coordinating the safety announcements of the competent authorities of the Member States;

(g) distributing appropriate information on pharmacovigilance concerns relating to medicinal products for human use to the general public, in particular by setting up and maintaining a European medicines web-portal;

(h) coordinating, as regards medicinal products for human use and veterinary medicinal products, the verification of compliance with the principles of good manufacturing practice, good laboratory practice, good clinical practice, good pharmacovigilance practice and, as regards medicinal products for human use, the verification of compliance with pharmacovigilance obligations;

(i) ensuring the secretariat of the Joint Audit Programme referred to in Article 54;

(j) upon request, providing technical and scientific support in order to improve cooperation between the Union, its Member States, international organisations and third countries on scientific and technical issues relating to the evaluation and monitoring of medicinal products for human use and of veterinary medicinal products, in particular in the framework of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the Veterinary International Conference on Harmonization;

(k) coordinating as referred to in Article 53 a structured cooperation on inspections in third countries between Member States, the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe, the World Health Organization or trusted international authorities, by means of international inspection programmes;

(l) **[**conducting inspections with Member States to verify the compliance with the principles of good manufacturing practice, including issuing GMP certificates and good clinical practice at the request of the Supervisory Authority referred to in Article 50(2) whenever additional capacity is needed to carry out inspection of Union interest including in response of public health emergencies;**]**

(m) recording the status of marketing authorisations for medicinal products for human use granted in accordance with Union marketing authorisation procedures;

(n) creating a database on medicinal products for human use, to be accessible to the general public, and ensuring that it is **technically** updated, and managed independently of pharmaceutical companies; the database is to facilitate the search for information already authorised for ~~package leaflets~~ **product information**; it is to include a section on medicinal products for human use authorised for the treatment of children; the information provided to the general public is to be worded in an appropriate and comprehensible manner;

(o) assisting the Union and its Member States in the provision of information to health-care professionals and the general public about medicinal products for human use and about veterinary medicinal products evaluated by the Agency;

(p) providing scientific advice to undertakings or, as relevant, not-for-profit entities on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products for human use;

(q) supporting, through enhanced scientific and regulatory advice, the development of medicinal products which are of major interest from the point of view of public health, including antimicrobial resistance, and in particular from the viewpoint of therapeutic innovation (priority medicines);

(r) checking that the conditions laid down in Union legal acts on medicinal products for human use and on veterinary medicinal products and in the marketing authorisations are met in the case of parallel distribution of medicinal products for human use and on veterinary medicinal products authorised in accordance with this Regulation or, as applicable, Regulation (EU) 2019/6;

(s) drawing up, at the Commission's request, any other scientific opinion concerning the evaluation of medicinal products for human use and of veterinary medicinal products or the starting materials used in the manufacture of medicinal products for human use;

(t) with a view to the protection of public health, compiling scientific information concerning pathogenic agents which might be used in biological warfare, including the existence of vaccines and other medicinal products for human use and other veterinary medicinal products available to prevent or treat the effects of such agents;

(u) coordinating the supervision of the quality of medicinal products for human use and of veterinary medicinal products placed on the market by requesting testing of compliance with their authorised specifications to the European Directorate for the Quality of Medicines and Healthcare that coordinates with the Official Medicines Control Laboratory or by a laboratory that a Member State has designated for that purpose. The Agency and the European Directorate for the Quality of Medicines and Healthcare shall enter into a written contract for the provision of services to the Agency under this subparagraph;

(v) forwarding annually to the budgetary authority aggregated information on procedures for medicinal products for human use and veterinary medicinal products;

(w) taking decisions as referred to in Article 6(5) of [revised Directive 2001/83/EC];

(x) contributing to the joint reporting with the European Food Safety Authority and European Centre for Disease Prevention and Control on the sales and use of antimicrobials in human and veterinary medicine as well as on the situation as regards antimicrobial resistance in the Union based on contributions received by Member States, taking into account the reporting requirements and periodicity in Article 57 of Regulation (EU) 2019/6. Such joint reporting shall be carried out at least every three years;

(y) **[**adopting a decision granting, refusing or transferring an orphan designation **in accordance with Articles 64- 66, 69 of the Regulation**;**]**

(z) adopting decisions on paediatric investigation plans, waivers and deferrals in relation to medicinal products **in accordance with Articles 74-76 of the Regulation**;

(za) providing regulatory support and scientific advice for the development of orphan and paediatric medicinal products **in accordance with Articles 68 and 89**;

(zb) coordinating assessment of and certifying quality master files for medicinal products for human use as well as, where necessary, coordinating inspections of manufacturers applying for or holding a certificate for a quality master file;

(zc) establishing a mechanism of consultation of authorities or bodies active along the life cycle of medicinal products for human use for exchange of information and pooling of knowledge on general issues of scientific or technical nature related to the tasks of the Agency;

(zd) developing coherent scientific assessment methodologies in the fields falling within its mission;

(ze) cooperating with EU decentralised agencies and other scientific authorities and bodies established under Union law, notably the European Chemicals Agency, the European Food Safety Authority, the European Centre for Disease Prevention and Control and the European Environment Agency as regards the scientific assessment of relevant substances, exchange of data and information and development of coherent scientific methodologies, including replacing, reducing or refining animal testing, taking into account the specificities of the assessment of medicinal products;

(zf) coordinating the monitoring and management of critical shortages of medicinal products included in the list referred to in Article 123(1);

(zg) coordinating the identification and management of the Union list of critical medicinal products referred to in Article 131;

(zh) **supporting the Commission and Member States** in relation to critical shortages and critical medicines **through** ~~supporting~~ the working party referred to in Article 121(1), point (c), and the MSSG ~~in their tasks in relation to critical shortages and critical medicines~~;

(zi) providing regulatory support and scientific advice for, and facilitate the development, validation and regulatory uptake of new-approach methodologies that replace the use of animals in testing;

(zj) facilitating joint non-clinical studies between applicants and holders to avoid unnecessary duplication of tests using live animals;

(zk) facilitating data sharing of results from non-clinical studies on live animals;

(zl) drawing up scientific guidelines to facilitate the implementation of the definitions established in this Regulation and in [revised Directive 2001/83], and for the environmental risk assessment of medicinal products for human use, in consultation with the Commission and the Member States.

2. The database provided for in paragraph 1, point (n), shall include all medicinal products for human use authorised in the Union together with the summaries of product characteristics, the package leaflet and the information shown on the labelling. Where relevant, it shall include the electronic links to the dedicated webpages where the marketing authorisation holders have reported the information pursuant to Article 40(4), point (b) **of this Regulation**, and Article 57 of [revised Directive 2001/83/EC].

For the purposes of the database, the Agency shall set up and maintain a list of all medicinal products for human use authorised in the Union. To this effect:

(a) the Agency shall make public a format for the electronic submission of information on medicinal products for human use;

(b) marketing authorisation holders shall electronically submit to the Agency information on all medicinal products for human use authorised in the Union and shall inform the Agency of any new or varied marketing authorisations granted in the Union, using the format referred to in point (a).

Where appropriate, the database shall also include references to clinical trials currently being carried out or already completed, contained in the clinical trials database provided for in Article 81 of Regulation (EU) No 536/2014.

The Commission is empowered to adopt delegated acts in accordance with Article 175, to supplement this Regulation by adding further information contained in the database, as well as by the specifying the rules of updating and maintenance of the data in the database. When adopting the delegated act, the Commission shall take into account internationally recognized standards.

Article 139

Coherence of scientific opinions with other Union bodies

1. The Agency shall take the necessary and appropriate measures to monitor and identify at an early stage any potential source of divergence between its scientific opinions and the scientific opinions issued by other Union bodies**,** ~~and~~ agencies **or scientific committee** carrying out similar tasks in relation to issues of common concern.

2. Where the Agency identifies a potential source of divergence, it shall contact the **Union** body ~~or~~**,** agency **or scientific committee** in question to ensure that all relevant scientific or technical information is shared and in order to identify potentially contentious scientific or technical issues.

3. Where a substantive divergence over scientific or technical issues is identified and the body concerned is a Union **Body or** Agency or a scientific committee, the Agency and the body**,** ~~agency~~ **or scientific committee** concerned shall cooperate to resolve the divergence, and inform the Commission without undue delay **and the Commission shall facilitate to resolve the divergence in question**.

4. The Commission may ask the Agency to conduct an assessment as regards specifically the use of the substance concerned in medicinal products. The Agency shall make public its assessment stating clearly the reasons for its specific scientific conclusions.

5. To enable coherence between scientific opinions and to avoid duplication of tests, the Agency shall make arrangements with other bodies or agencies established **or designated** under Union law for cooperation on scientific assessments and methodologies. The Agency shall also make arrangements for the exchange of data and information on relevant substances with the Commission, Member States' authorities and other Union Agencies, in particular for environmental risk assessments, non-clinical studies and**, when applicable,** maximum residue limits.

These arrangements shall seek to ensure that exchanges of data and information are made available in electronic formats and shall protect the commercially confidential nature of the information exchanged and be without prejudice to the provisions on regulatory protection.

Article 140

Scientific opinions in the context of international collaboration

1. The Agency may give a scientific opinion, in particular in the context of cooperation with the World Health Organization, for the evaluation of certain medicinal products for human use intended for markets outside the Union. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. Such application may be submitted and assessed together with a marketing authorisation application or any subsequent variation for the EU. The Agency may, after consulting the World Health Organization, and as appropriate other relevant organisations, draw up a scientific opinion in accordance with Articles 6, 10 and 12. The provisions of Article 13 shall not apply.

2. The Agency shall establish specific procedural rules for the implementation of paragraph 1, as well as for the provision of scientific advice.

Article 141

International regulatory cooperation

1. In so far as is necessary in order to achieve the objectives set out in this Regulation, and without prejudice to the respective competences of the Member States and the institutions of the Union, the Agency may cooperate with the competent authorities of third countries and/or with international organisations.

   To this end, the Agency may, subject to prior approval by the Commission, establish working arrangements with the authorities of third countries and international organisations, with regard to:

   (a) the exchange of information, including non-public information, where relevant jointly with the Commission;
   (b) sharing of scientific resources and expertise, with a view to facilitating collaboration, while maintaining independent assessment in full compliance with the provisions of this Regulation and [revised Directive 2001/83/EC] and under conditions determined beforehand by the Management Board, in agreement with the Commission;
   (c) the participation in certain aspects of the Agency's work, under conditions determined beforehand by the Management Board, in agreement with the Commission.

   These arrangements shall not create legal obligations incumbent on the Union and its Member States.

2. The Agency shall ensure that it is not seen as representing the Union position to an outside audience or as committing the Union to international cooperation.

3. The Commission may, in agreement with the Management Board and the relevant committee, invite representatives of international organisations with an interest in the harmonisation of technical requirements applicable to medicinal products for human use and to veterinary medicinal products to participate as observers in the work of the Agency. The conditions for participation shall be determined in advance by the Commission.

Section 2

Structure and operation

Article 142

Administrative and management structure

The Agency shall comprise:

(a) a Management Board, which shall exercise the functions set out in Articles 143, 144 and 154.

(b) an Executive Director, who shall exercise the responsibilities set out in Article 145;

(c) a Deputy Executive Director who shall exercise the responsibilities set out in Article 145(7);

(d) the Committee for Medicinal Products for Human Use;

(e) the Pharmacovigilance Risk Assessment Committee;

(f) the Committee for Veterinary Medicinal Products set up pursuant to Article 139(1) of Regulation (EU) 2019/6;

(g) the Herbal Medicinal Products working group set up pursuant to Article 141 of [revised Directive 2001/83/EC];

(h) the Emergency task force set up pursuant to Article 15 of Regulation (EU) 2022/123;

(i) the **Medicines Shortages Steering Group (**MSSG**)** set up pursuant to Article 3 of Regulation (EU) 2022/123;

(j) the Medical Device Shortages Steering Group, set up pursuant to Article 21 of Regulation (EU) 2022/123;

(k) **[**the inspection**s** working group**]**;

(l) a Secretariat, which shall provide technical, scientific and administrative support to all bodies of the Agency and ensure appropriate coordination between them, and which shall provide technical and administrative support for the coordination group referred to in Article 37 of [revised Directive 2001/83/EC] and ensure appropriate coordination between it and the Committees. It shall also undertake the work required of the Agency under the procedures for the assessment and preparations of decisions for paediatric investigation plans, waivers, deferrals or orphan designations.

Article 143

Management Board

1. The Management Board shall be composed of one representative from each Member State, two representatives of the Commission and two representatives of the European Parliament, all with voting rights.

   In addition, two representatives of patients' organisations, one representative of ~~doctors'~~ **healthcare professionals'** organisations and one representative of veterinarians' organisations, all with voting rights, shall be appointed by the Council in consultation with the European Parliament on the basis of a list drawn up by the Commission which includes appreciably more names than there are posts to be filled. The list drawn up by the Commission shall be forwarded to the European Parliament, together with the relevant background documents. As quickly as possible, and at the latest within three months of notification, the European Parliament may submit its views for consideration to the Council, which shall then appoint these representatives to the Management Board.

   The members of the Management Board shall be appointed in such a way as to guarantee the highest levels of specialist qualifications, a broad spectrum of relevant expertise and the broadest possible geographic spread within the European Union.

2. Members of the Management Board and their alternates shall be appointed on the basis of their knowledge, recognised experience and commitment in the field of medicinal products for human or veterinary use, taking into account relevant managerial, administrative and budgetary expertise [which are to be used to further the objectives of this Regulation].

   All parties represented in the Management Board shall make efforts to limit turnover of their representatives, in order to ensure continuity of the work of the Management Board. All parties shall aim to achieve a balanced representation between men and women on the Management Board.

3. Each Member State and the Commission shall appoint their members of the Management Board as well as an alternate who will replace the member in their absence and vote on their behalf.

4. The term of office for members and their alternates shall be four years. That term shall be extendable.

5. The Management Board shall elect a chairperson and a Deputy chairperson from among its members.

   The chairperson and the Deputy chairperson shall be elected by a majority of two-thirds of the members of the Management Board with voting rights.

   The Deputy chairperson shall automatically replace the chairperson if they are prevented from attending to their duties.

   The term of office of the chairperson and the deputy chairperson shall be four years. The term of office may be renewed once. If however, their membership of the Management Board ends at any time during their term of office, their term of office shall automatically expire on that date.

6. Without prejudice to paragraph 5 and Article 144, points (e) and (g), the Management Board shall take decisions by absolute majority of its members with voting rights.

7. The Management Board shall adopt its rules of procedure.

8. The Management Board may invite the chairpersons of the scientific committees to attend its meetings, but they shall not have the right to vote.

9. The Management Board may invite any person whose opinion may be of interest to attend its meetings as an observer.

10. The Management Board shall approve the annual work programme of the Agency programme and forward it to the European Parliament, the Council, the Commission and the Member States.

11. The Management Board shall adopt the annual report on the Agency's activities and forward it by 15 June at the latest to the European Parliament, the Council, the Commission, the European Economic and Social Committee, the Court of Auditors and the Member States.

Article 144

Tasks of the Management Board

The Management Board shall:

(a) give the general orientations for the Agency's activities;

(b) adopt an opinion on the rules of procedures of the Committee for Medicinal Products for Human Use (Article 148) and the Committee for Veterinary Medicinal Products (Article 139 of Regulation (EU) 2019/6) (c) adopt procedures for the performance of scientific services regarding medicinal products for human use (Article 152);

(d) appoint the Executive Director **and the Deputy Executive Director**, and where relevant ~~extend~~ **renew** their term of office or remove them from office, in accordance with Article 145;

(e) adopt yearly the Agency's draft single programming document before its submission to the Commission for its opinion, and the Agency's single programming document by a majority of two-thirds of members entitled to vote and in accordance with Article 154;

(f) assess and adopt a consolidated annual activity report on the Agency's activities and send it by 1 July each year to the European Parliament, the Council, the Commission and the Court of Auditors. The consolidated annual activity report shall be made public;

(g) adopt the annual budget of the Agency by a majority of two-thirds of the members entitled to vote and in accordance with Article 154;

(h) adopt the financial rules applicable to the Agency in accordance with Article 155;

(i) exercise, with respect to the staff of the Agency, the powers conferred by Regulation No 31 by the Council of the European Economic Community, and Regulation No 11 and by the Council of the European Atomic Energy Community ('Staff Regulations' and 'Conditions of Employment of Other Servants')[54] on the Appointing Authority and on the Authority Empowered to Conclude a Contract of Employment ('the appointing authority powers');

(j) adopt implementing rules for giving effect to the Staff Regulations and the Conditions of Employment of Other Servants in accordance with Article 110 of the Staff Regulations;

(k) develop contacts with stakeholders and stipulate the conditions applicable as mentioned in Article 163;

(l) adopt an anti-fraud strategy, proportionate to risks of fraud taking into account the costs and benefits of the measures to be implemented;

(m) ensure adequate follow-up to findings and recommendations stemming from the internal or external audit reports and evaluations, as well as from investigations of the European Anti-fraud Office ('OLAF') and the European Public Prosecutor's Office ('EPPO');

(n) adopt rules to ensure the availability to the public of information concerning the authorisation or supervision of medicinal products for human use as mentioned in Article 166;

(o) adopt an efficiency gains and synergies strategy;

(p) adopt a strategy for cooperation with third countries or international organisations **within the limits of the Agency's mandate**;

(q) adopt **and** ~~a~~ **implement a** strategy for the organisational management and internal control systems **with particular regard to the operation of the Committees, scientific working parties and scientific advisory groups in relation to efficiency as well as scientific expertise and geographic representation of experts**~~.~~**;**

[54] Regulation No 31 (EEC), 11 (EAEC) by the Council of the European Economic Community and by the Council of the European Atomic Energy Community, laying down the Staff Regulations of Officials and the Conditions of Employment of Other Servants of the European Economic Community and the European Atomic Energy Community (OJ 45, 14.6.1962, p. 1385).

(qa) assess and adopt a report regarding of the performance of the strategy referred in point q in every three years following the entry into force of this Regulation. The report shall, amongst others, contain quantitative data on the involvement of scientific expertise related to marketing authorisation application assessment and the provision of regulatory and scientific advice for paediatric and orphan medicinal products, ATMPs and evaluation of environmental risks asessment as well as on the work-share and task distribution between experts nominated by the national competent authorities and external experts.

The Management Board shall adopt, in accordance with Article 110 of the Staff Regulations, a decision based on Article 2(1) of the Staff Regulations and on Article 6 of the Conditions of Employment of Other Servants, delegating relevant appointing authority powers to the Executive Director **and Deputy Executive Director** and defining the conditions under which that delegation of powers can be suspended. The Executive Director shall be authorised to sub-delegate those powers.

Where exceptional circumstances so require, the Management Board may, by way of a decision, temporarily suspend the delegation of the appointing authority powers to the Executive Director and those sub-delegated by the latter and exercise them itself or delegate them to one of its members or to a staff member other than the Executive Director.

Article 145

Executive Director

1. The Executive Director shall be engaged as a temporary agent of the Agency under Article 2, point (a), of the Conditions of Employment of Other Servants.

2. The Executive Director shall be appointed by the Management Board from a list of candidates proposed by the Commission following an open and transparent selection procedure.

   For the purpose of concluding the contract with the Executive Director, the Agency shall be represented by the Chairperson of the Management Board.

Before appointment, the candidate nominated by the Management Board shall be immediately invited to make a statement to the European Parliament and to answer any questions put by its Members.

3. The term of office of the Executive Director shall be five years. By the end of that period the Commission shall undertake an assessment that takes into account an evaluation of the Executive Director's performance and the Agency's future tasks and challenges.

4. The Management Board, acting on a proposal from the Commission that takes into account the assessment referred to in paragraph 3, may extend the term of office of the Executive Director once, for no more than five years.

   An Executive Director whose term of office has been extended may not participate in another selection procedure for the same post at the end of the overall period.

5. The Executive Director may be removed from office only upon a decision of the Management Board acting on a proposal from the Commission.

6. The Management Board shall reach decisions on appointment, extension of the term of office or removal from office of the Executive Director on the basis of a two-thirds majority of its members with voting rights.

7. The Executive Director will be assisted by a Deputy Executive Director. If the Executive Director is absent or indisposed, the Deputy Executive Director shall take their place.

8. The Executive Director shall manage the Agency. The Executive Director shall be accountable to the Management Board. Without prejudice to the powers of the Commission and of the Management Board, the Executive Director shall be independent in the performance of their duties and shall neither seek nor take instructions from any government or from any other body.

9. The Executive Director shall report to the European Parliament on the performance of their tasks when invited to do so. The Council may invite the Executive Director to report on the performance of those tasks.

10. The Executive Director shall be the legal representative of the Agency. The Executive Director shall be responsible for:
    (a) the day-to-day administration of the Agency;
    (b) implementing decisions adopted by the Management Board;
    (c) managing all the Agency resources necessary for conducting the activities of the Committees referred to in Article 142, including making available appropriate scientific and technical support to those Committees, and for making available appropriate technical support to the coordination group **referred to in Article 37 of [revised Directive 2001/83/EC];**;
    (d) ensuring that the time-limits laid down in Union legal acts for the adoption of opinions by the Agency are complied with;
    (e) ensuring appropriate coordination between the Committees referred to in Article 142 and, where necessary, between those Committees and the coordination group **referred to in Article 37 of [revised Directive 2001/83/EC];** or other working groups of the Agency;
    (f) the preparation of the draft statement of estimates of the Agency's revenue and expenditure, and execution of its budget;
    (g) the preparation of the draft single programming document and the submission it to the Management Board after consulting the Commission;
    (h) implementing the single programming document and report to the Management Board on its implementation;
    (i) preparing the Agency's consolidated annual activity report on the Agency's activities and presenting it to the Management Board for assessment and adoption;
    (j) all staff matters;
    (k) providing the secretariat for the Management Board;

(l) without prejudice to the competences of OLAF and EPPO, protecting the financial interests of the Union by applying preventive measures against fraud, corruption and any other illegal activities, by effective checks and, if irregularities are detected, by recovering amounts wrongly paid and, where appropriate, by imposing effective, proportionate and dissuasive administrative and financial penalties;

(m) reporting, on the basis of key performance indicators agreed by the Management board, on the IT infrastructure developed by the Agency by means of implementation of legislation, in term of timing, budgetary compliance and quality.

11. Each year the Executive Director shall submit a draft report covering the activities of the Agency in the previous year and a draft work programme for the coming year to the Management Board for approval, making a distinction between the Agency's activities concerning medicinal products for human use, those concerning herbal medicinal products and those concerning veterinary medicinal products.

The draft report covering the activities of the Agency in the previous year shall include information about the number of applications evaluated by the Agency, the time taken for completion of the evaluation, and the medicinal products for human use and veterinary medicinal products authorised, rejected or withdrawn.

Article 145a

Deputy Executive Director

~~1.~~ **On the proposal of the Executive Director, the Management Board shall appoint the Deputy Executive Director. The Deputy Executive Director shall be appointed on the grounds of merit and appropriate administrative and management skills, including relevant professional experience. The Executive Director shall, following consultation with the Commission, propose at least three candidates for the post of Deputy Executive Director. The Management Board shall take its decision by a two-thirds majority of its members with a right to vote. The Management Board shall have the power to dismiss the Deputy Executive Director by means of a decision adopted by a two-thirds majority of its members with a right to vote.**

The term of office of the Deputy Executive Director shall be five years. The Management Board may extend that term once, for a period of no more than five years. The Management Board shall adopt such a decision by a two-thirds majority of its members with the right to vote.

~~**The Management Board shall appoint a Deputy Executive Director to assist the Executive Directorprovisions of Article 145 shall apply to the Deputy Executive Director accordingly.**~~

~~**2. The provisions of Article 145 shall apply to the Deputy Executive Director accordingly.**~~

Article 146

Scientific Committees – General provisions

1. The scientific committees shall be responsible for providing the scientific opinions or recommendations of the Agency, each within their own spheres of competence, and shall have the possibility, where necessary of organising public hearings.

2. The membership of the scientific committees shall be made public. When each appointment is published, the professional qualifications of each member shall be specified.

3. The Executive Director of the Agency or their representative and representatives of the Commission shall be entitled to attend all meetings of the scientific committees referred to in Article 142, working parties and scientific advisory groups and all other meetings convened by the Agency or its scientific committees.

4. Members of the scientific committees and experts responsible for evaluating medicinal products and nominated by Member States shall rely on the scientific evaluation and resources available to national competent authorities responsible for marketing authorisation, and on external experts proposed by Member States or selected by the Agency. Each competent national authority shall monitor the scientific level and independence of the evaluation carried out and facilitate the activities of nominated members of the Committees and experts. Member States shall refrain from giving those members and experts any instruction which is incompatible with their own individual tasks or with the tasks and responsibilities of the Agency.

5. The members of the scientific committees may be accompanied by experts in specific scientific or technical fields.

6. When preparing any opinion or recommendation, the scientific committees shall use their best endeavours to reach a scientific consensus. If such a consensus cannot be reached, the opinion shall consist of the position of the majority of members and divergent positions, with the grounds on which they are based.

7. The **scientific** ~~Committee~~ **committees** ~~for Medicinal Products for Human Use~~ may, if they consider it appropriate, seek guidance on important questions of a general scientific or ethical nature.

8. The scientific committees and any **scientific** working parties and scientific advisory groups established in accordance with ~~this~~ Article **150** shall in general matters establish contacts, on an advisory basis, with parties concerned with the use of medicinal products for human use, in particular patient and consumer organisations and healthcare professionals' associations. For that purpose working groups of patient and consumer organisations and healthcare professionals' associations shall be established by the Agency. They shall ensure a fair representation of healthcare professionals, patients and consumers covering a wide range of experience and disease areas, including orphan, paediatric and geriatric diseases and advanced therapy medicinal products, and a broad geographical range.

   Rapporteurs appointed by the scientific committees may, on an advisory basis, establish contacts with representatives of patient organisations and healthcare professionals' associations relevant to the therapeutic indication of the medicinal product for human use.

9. The Committee for Veterinary Medicinal Products shall operate in accordance with Regulation (EU) No 2019/6 and paragraphs 1, 2 and 3.

Article 147

Conflict of interest

1. Members of the Management Board, members of the committees, rapporteurs and experts shall not have financial or other interests in the pharmaceutical industry**, clinical research organisations, medical devices industry or biotechnology sector** which could affect their impartiality. They shall undertake to act in the public interest and in an independent manner, and shall make an annual declaration of their financial interests. All indirect interests which could relate to this industry shall be entered in a register held by the Agency which is accessible to the public, on request, at the Agency's offices.

   The Agency's code of conduct shall provide for the implementation of this Article with particular reference to the acceptance of gifts.

2. Members of the Management Board, members of the committees, rapporteurs and experts who participate in meetings or working groups of the Agency shall declare, at each meeting, any specific interests which could be considered to be prejudicial to their independence with respect to the items on the agenda. These declarations shall be made available to the public.

Article 148

Committee for Medicinal Products for Human Use activities

1. The Committee for Medicinal Products for Human Use shall be responsible for drawing up the opinion of the Agency on any matter concerning the admissibility of the files submitted in accordance with the centralised procedure, the granting, variation, suspension or revocation of an authorisation to place a medicinal product for human use on the market in accordance with the provisions of this Chapter, ~~and~~ pharmacovigilance **and scientific advice**. For the fulfilment of its pharmacovigilance tasks, including the approval of risk management systems and monitoring their effectiveness provided for under this Regulation, the Committee for Medicinal Products for Human Use shall rely on the scientific assessment and recommendations of the Pharmacovigilance Risk Assessment Committee referred to in Article 142, point (e).

2. In addition to their task of providing objective scientific opinions to the Union and Member States on the questions which are referred to them, the members of the Committee for Medicinal Products for Human Use shall ensure that there is appropriate coordination between the tasks of the Agency and the work of competent national authorities, including the consultative bodies concerned with the marketing authorisation.

3. The Committee for Medicinal Products for Human Use shall be composed of the following:
   (a) one member and one alternate member appointed by each Member State, in accordance with paragraph 6;
   (b) four members and ~~one~~ **four** **two** alternate members appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent healthcare professionals**' organisations**;

(c) four members and four alternate members appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent patient organisations.

Members under paragraph 3.b. and 3.c shall be appointed by the Commission to represent relevant expertise or experience, including inter alia those, which relate to rare paediatric diseases and advanced therapy medicinal products.

4. The Committee for Medicinal Products for Human Use may co-opt a maximum of **seven** ~~five~~ additional members chosen on the basis of their specific scientific competence. Those members shall be appointed for a term of three years, which may be renewed, and shall not have alternates.

With a view to the co-opting of such members, the Committee for Medicinal Products for Human Use shall identify the specific complementary scientific competence of the additional member or members. Co-opted members shall be chosen among experts nominated by Member States or the Agency.

4a. In the deliberations of the Committee for Medicinal Products for Human Use shall take into account the opinion of Members appointed under paragraphs 3 b and c, but only the Members appointed under paragraph 3.a. and 4 may participate with voting rights.

5. The alternates shall represent and vote for the members in their absence and may also be appointed to act as rapporteurs in accordance with Article 152.

Members and alternates shall be chosen for their role and experience in the evaluation of medicinal products for human use as appropriate and shall represent the competent authorities of the Member States.

6. The members and alternate members of the Committee for Medicinal Products for Human Use shall be appointed on the basis of their relevant expertise in the assessment of medicinal products**.** which should cover all types of medicinal products covered by [revised Directive 2001/83/EC] and this Regulation and which include medicinal products for rare and paediatric diseases, advance therapy medicinal products, biological and biotechnological products~~,~~ in order to guarantee the highest levels of specialist qualifications and a broad spectrum of relevant expertise. **This expertise shall also cover the environmental risk assessment.** The Member States shall cooperate in order to ensure that the final composition of the Committee for Medicinal Products for Human Use provides appropriate and balanced coverage of all scientific areas relevant to its tasks taking into account scientific developments and new types of medicinal products. For this purpose, Member States shall liaise with the Management Board ~~and the Commission~~.

7. The members and alternate members of the Committee for Medicinal Products for Human Use shall be appointed for a term of th**r**ee years, which may be renewed following the procedures referred to in paragraph 6. The Committee shall elect its chairperson and vice-chairperson from among its members for a term of 3 years, which may be prolonged once.

8. The Committee for Medicinal Products for Human Use shall establish its own rules of procedure.

These rules shall, in particular, lay down:

(a) procedures for appointing and replacing the chairperson;

(b) procedures relating to working parties and scientific advisory groups; and

(c) a procedure for the urgent adoption of opinions, particularly in relation to the provisions of this Regulation on market surveillance and pharmacovigilance.

They shall enter into force after receiving a favourable opinion from the Commission and the Management Board.

Article 149

Pharmacovigilance Risk Assessment Committee activities

1. The mandate of the Pharmacovigilance Risk Assessment Committee shall cover all aspects of the risk management of the use of medicinal products for human use including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product for human use, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit.

2. The Pharmacovigilance Risk Assessment Committee shall be composed of the following:
   (a) one member and one alternate member appointed by each Member State, in accordance with paragraph 3;
   (b) six members appointed by the Commission, with a view to ensuring that the relevant expertise is available within the Committee, including clinical pharmacology and pharmacoepidemiology, on the basis of a public call for expressions of interest**. To this end the Pharmacovigilance Risk Assessment Committee shall identify the specific complementary scientific competence of the additional member or members**;
   (c) two members and two alternate members appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent healthcare professionals**' organisations**;
   (d) two members and two alternate members appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent patient organisations.

   The alternate members shall represent and vote for the members in their absence. The alternate members referred to in point (a) may be appointed to act as rapporteurs in accordance with Article 152.

3. A Member State may delegate its tasks in the Pharmacovigilance Risk Assessment Committee to another Member State. Each Member State may represent no more than one other Member State.

3a. In the deliberations of the Pharmacovigilance Risk Assessment Committee only the Members appointed under paragraph 2.a. and 2.d. may participate with voting rights.

4. The members and alternate members of the Pharmacovigilance Risk Assessment Committee shall be appointed on the basis of their relevant expertise in pharmacovigilance matters and risk assessment of medicinal products for human use, in order to guarantee the highest levels of specialist qualifications and a broad spectrum of relevant expertise. For this purpose, Member States shall liaise with the Management Board and the Commission in order to ensure that the final composition of the Committee covers the scientific areas relevant to its tasks.

5. The members and alternate members of the Pharmacovigilance Risk Assessment Committee shall be appointed for a term of 3 years, which may be renewed ~~following the procedures referred to in paragraph 1~~. The Committee shall elect its chairperson and vice-chairperson from among its members for a term of three years, which may be prolonged once.

Article 150

Scientific working parties and scientific advisory groups

1. The scientific committees referred to in Article 146 may establish scientific working parties and scientific advisory groups in connection with the performance of their tasks.

The scientific committees may rely on scientific working parties for the performance of certain tasks. The scientific committees shall retain the final responsibility for the assessment or any scientific opinion related to these tasks.

Working parties established by the Committee for Veterinary Medicinal Products are governed by Regulation (EU) 2019/6.

2. The Committee for Human Medicinal Products shall establish for the evaluation of specific types of medicinal products or treatments, working parties with scientific expertise in the fields of pharmaceutical quality, methodologies, non-clinical and clinical evaluations. **When establishing working parties, the Committee shall ensure that necessary expertise in the field of orphan and paediatric medicinal products is appropriately represented.**

   For the provision of scientific advice the Committee for Human Medicinal Products shall establish a scientific advice working party.

   The Committee may establish an Environmental Risk Assessment working party and other scientific working parties, as necessary.

3. The composition of the working party and the selection of members shall be based on the following criteria:
   (a) a high level of scientific expertise;
   (b) meeting the needs for the specific multi-disciplinary expertise of the working party to which they will be appointed.

   The majority of the members of the working parties shall consist of experts from the competent authorities of the Member States **by ensuring the broadest possible** ~~**representation from the Member States**~~ **geographical distribution**. **Where a specific area for expertise can be fulfilled by an expert nominated by a competent authority of a Member State, this expert shall have priority over external experts.** Where appropriate, the Committee for Human Medicinal Products may, following consultation with the Management Board, set a minimum number of experts from the competent authorities in a working party.

4. Competent authorities of the Member States that are not represented in a working party may ~~request to~~ attend meetings of working parties as an observer.

4a. The Committee may consult scientific advisory groups in connection with the evaluation of specific types of medicinal products or treatments when drawing up the scientific opinions referred to in Art. 148.1.

5. The Agency shall make documents discussed in working parties accessible to all competent authorities of the Member States.

6. When establishing working parties and scientific advisory groups, the scientific committees shall in their rules of procedures provide for:
   (a) the appointment of members of these working parties and scientific advisory groups on the basis of the lists of experts referred to in Article 151(2); and
   (b) consultation of these working parties and scientific advisory groups.

Article 151

Scientific experts

1. The Agency or any of the committees referred to in Article 142 may use the services of experts and service providers for the discharge of specific tasks for which they are responsible.

2. Member States shall transmit to the Agency the names of national experts with ~~proven~~ **validated** experience in the evaluation of medicinal products for human use and veterinary medicinal products who, taking into account conflicts of interest pursuant to Article 147, would be available to serve on working parties or scientific advisory groups of any of the committees referred to in Article 142, together with an indication of their qualifications and specific areas of expertise.

3. Where necessary, for the nomination of other experts the Agency may publish a call for expression of interest after endorsement by the Management Board of the necessary criteria and fields of expertise, in particular to ensure a high level of public health and animal protection.

The Management Board shall adopt the appropriate **selection and validation** procedures on a proposal from the Executive Director.

4. The Agency shall establish and maintain a pool of ~~accredited~~ experts **validated by the Member States or the Agency in accordance with paragraphs (2) and (3)**. That expert pool shall include the national experts referred to in paragraph 2 and any other experts appointed by the Agency or the Commission, and shall be updated.

5. ~~Accredited~~ **Validated** experts shall have access to training provided by the Agency, as appropriate.

6. Rapporteurs of any of the committees referred to in Article 142 may use the services of ~~accredited~~ **validated** experts for the fulfilment of their tasks in accordance with Article 152. Any remuneration of such ~~accredited~~ **validated** expert shall be deducted from the remuneration due to the rapporteurs.

7. The remuneration of **validated** experts and service providers for services used by the Agency under paragraph 1 shall be financed through the Agency's budget, in accordance with the financial rules applicable to the Agency.

Article 152

Rapporteurship

1. Where, in accordance with this Regulation, any of the Committees referred to in Article 142 is required to evaluate a medicinal product for human use, it shall appoint**, with the exception of members representing healthcare professionals' organisations and patients organisations,** one of its members to act as rapporteur, taking into account existing expertise in the Member State. The Committee concerned may appoint a second member to act as co-rapporteur.

A member of a Committee shall not be appointed rapporteur for a particular case if they declare, in accordance with Article 147 any interest that might be, or might be **reasonably** perceived as, prejudicial to the impartial assessment of that case. The Committee concerned may replace the rapporteur or co-rapporteur by another member at any time, if they are unable to fulfil their duties within the prescribed time limits, or if an actual or potential prejudicial interest is detected.

A rapporteur appointed for that purpose by the Pharmacovigilance Risk Assessment Committee shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use or the Reference Member State for the medicinal product for human use concerned.

When consulting the scientific advisory groups referred to in Article 150, the Committee shall forward to them the draft assessment report ~~or~~ **and** reports drawn up by the rapporteur or the co-rapporteur. The opinion issued by the scientific advisory group shall be forwarded to the chairperson of the relevant committee in such a way as to ensure that the deadlines laid down in Article 6 are met.

The substance of the opinion shall be included in the assessment report published pursuant to Article 16(3).

2. Without prejudice to Article 151(7), the provision of services by rapporteurs or experts shall be governed by a written contract between the Agency and the person concerned, or where appropriate between the Agency and its employer.

The person concerned, or their employer, shall be remunerated in accordance with [a scale of fees to be included in the financial arrangements established by the Management Board/mechanism under the new fee legislation].
The first and second subparagraphs shall also apply:

(a) to the services provided by the chairpersons of the scientific committees of the Agency; and

(b) to the work of rapporteurs in the coordination group **referred to in Article 37 of [revised Directive 2001/83/EC]** as regards the fulfilment of its tasks in accordance with Articles 108, 110, 112, 116 and 121 of [revised Directive 2001/83/EC].

Article 153

Methods to determine added therapeutic value

At the request of the Commission, the Agency shall, in respect of authorised medicinal products for human use, collect any available information on methods that Member States' competent authorities use to determine the added therapeutic value that any new medicinal product for human use provides.

Section 3

Financial provisions

Article 154

Adoption of the budget of the Agency

1. Estimates of all the revenue and expenditure of the Agency shall be prepared for each financial year, corresponding to the calendar year, and shall be shown in the budget of the Agency.

2. The revenue and expenditure shown in the budget shall be in balance.

3. The Agency's revenue shall consist of:
   (a) a contribution from the Union;
   (b) a contribution from third countries participating in the work of the Agency with which the Union has concluded international agreements for that purpose;

(c) fees paid by undertakings and entities not engaged in an economic activity:
   (i) for obtaining and maintaining Union marketing authorisations for medicinal products for human use and for veterinary medicinal products and for other services provided by the Agency, as provided for in this Regulation and in Regulation (EU) 2019/6; and
   (ii) for services provided by the coordination group **referred to in Article 37 of [revised Directive 2001/83/EC]** as regards the fulfilment of its tasks in accordance with Articles 108, 110, 112, 116 and 121 of [revised Directive 2001/83/EC];
(d) charges for other services provided by the Agency;
(e) Union funding in the form of grants for participation in research and assistance projects, in accordance with the Agency's financial rules referred to in Article 155(11) and with the provisions of the relevant instruments supporting the policies of the Union.

The European Parliament and the Council ('the budgetary authority') shall re-examine, when necessary, the level of the Union contribution, referred to in the first subparagraph, point (a), on the basis of an evaluation of needs and by taking account of the level of revenue provided by the sources referred to in the first subparagraph, points (c), (d) and (e).

4. Activities relating to the assessment of marketing authorisation applications, subsequent variations, pharmacovigilance, to the operation of communications networks and to market surveillance shall be under the permanent **financial** control of the Management Board in order to guarantee the independence of the Agency. This shall not preclude the Agency from charging fees to marketing authorisation holders for performing these activities by the Agency on the condition that its independence is strictly guaranteed.

5. The expenditure of the Agency shall include staff remuneration, administrative and infrastructure costs, and operational expenditure. In respect of operational expenditure, budgetary commitments for actions which extend over more than one financial year may be broken down over several years into annual instalments, as necessary.

The Agency may award grants related to the fulfilment of the tasks incumbent upon it under this Regulation or other relevant Union legal acts or related to the fulfilment of other entrusted tasks.

6. Each year the Management Board, on the basis of a draft drawn up by the Executive Director, shall produce an estimate of revenue and expenditure for the Agency for the following financial year. That estimate, which shall include a draft establishment plan, shall be forwarded by the Management Board to the Commission by 31 March at the latest.

7. The estimate shall be forwarded by the Commission to the budgetary authority together with the preliminary draft general budget of the European Union.

8. On the basis of the estimate, the Commission shall enter in the preliminary draft general budget of the European Union the estimates it deems necessary for the establishment plan and the amount of the subsidy to be charged to the general budget, which it shall place before the budgetary authority in accordance with Article 272 of the Treaty.

9. The budgetary authority shall authorise the appropriations for the subsidy to the Agency.

   The budgetary authority shall adopt the establishment plan for the Agency.

10. The budget shall be adopted by the Management Board. It shall become final following final adoption of the general budget of the European Union. Where appropriate, it shall be adjusted accordingly.

11. Any modification of the establishment plan and of the budget shall be the subject of an amending budget, which is forwarded for the purposes of information to the budgetary authority.

12. The Management Board shall, as soon as possible, notify the budgetary authority of its intention to implement any project which may have significant financial implications for the funding of its budget, in particular any projects relating to property such as the rental or purchase of buildings. It shall inform the Commission thereof.

    Where a branch of the budgetary authority has notified its intention to deliver an opinion, it shall forward its opinion to the Management Board within a period of six weeks from the date of notification of the project.

Article 155
Implementation of the Agency's budget

1. The Executive Director shall implement the budget of the Agency in accordance with Regulation (EU, Euratom) 2018/1046 of the European Parliament and of the Council[55].

2. By 1 March of financial year n+1, the Agency's accounting officer shall send the provisional accounts for year n to the Commission's accounting officer and to the Court of Auditors.

3. By 31 March of financial year n+1, the Executive Director shall send the report on the budgetary and financial management for year n to the European Parliament, to the Council, to the Commission and to the Court of Auditors.

4. By 31 March of financial year n+1, the Commission's accounting officer shall send the Agency's provisional accounts for year n, consolidated with the Commission's provisional accounts, to the Court of Auditors.

55 Regulation (EU, Euratom) 2018/1046 of the European Parliament and of the Council of 18 July 2018 on the financial rules applicable to the general budget of the Union, amending Regulations (EU) No 1296/2013, (EU) No 1301/2013, (EU) No 1303/2013, (EU) No 1304/2013, (EU) No 1309/2013, (EU) No 1316/2013, (EU) No 223/2014, (EU) No 283/2014, and Decision No 541/2014/EU and repealing Regulation (EU, Euratom) No 966/2012 (OJ L 193, 30.7.2018, p. 1).

On receipt of the Court of Auditors' observations on the Agency's provisional accounts pursuant to Article 246 of Regulation (EU, Euratom) 2018/1046, the Agency's accounting officer shall draw up the Agency's final accounts and the Executive Director shall submit them to the Management Board for an opinion.

5. The Management Board shall deliver an opinion on the Agency's final accounts for year n.

6. The Agency's accounting officer shall, by 1 July of financial year n+1, send the final accounts, together with the Management Board's opinion, to the European Parliament, to the Council, to the Court of Auditors and to the Commission's accounting officer.

7. The final accounts for year n shall be published in the *Official Journal of the European Union* by 15 November of financial year n+1.

8. The Executive Director shall send to the Court of Auditors a reply to its observations by 30 September of financial year n+1. The Executive Director shall also send that reply to the Management Board.

9. The Executive Director shall submit to the European Parliament, at the latter's request, any information required for the smooth application of the discharge procedure for the financial year concerned, as laid down in Article 261(3) of Regulation (EU, Euratom) 2018/1046.

10. The European Parliament, upon a recommendation from the Council, shall, before 15 May of financial year n+2, give a discharge to the Executive Director in respect of the implementation of the budget for year n.

11. The financial rules applicable to the Agency shall be adopted by the Management Board after the Commission has been consulted. They shall not depart from Commission Delegated Regulation (EU) 2019/715[56] unless specifically required for the Agency's operation and with the Commission's prior consent.

Article 156
Fraud prevention

1. In order to combat fraud, corruption and other unlawful activities, the Regulation (EU, Euratom) No 883/2013 of the European Parliament and of the Council[57] shall apply without restriction.

2. The Agency shall accede to the Interinstitutional Agreement of 25 May 1999 between the European Parliament, the Council of the European Union and the Commission of the European Communities[58] and shall adopt, without delay, the appropriate provisions applicable to all the employees of the Agency using the template set out in the Annex to that Agreement.

3. The European Court of Auditors shall have the power of audit, on the basis of documents and on the spot, over all grant beneficiaries, contractors and subcontractors who have received Union funds from the Agency.

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56 Commission Delegated Regulation (EU) 2019/715 of 18 December 2018 on the framework financial regulation for the bodies set up under the TFEU and Euratom Treaty and referred to in Article 70 of Regulation (EU, Euratom) 2018/1046 of the European Parliament and of the Council (OJ L 122, 10.5.2019, p. 1).

57 Regulation (EU, Euratom) No 883/2013 of the European Parliament and of the Council of 11 September 2013 concerning investigations conducted by the European Anti-Fraud Office (OLAF) and repealing Regulation (EC) No 1073/1999 of the European Parliament and of the Council and Council Regulation (Euratom) No 1074/1999 (OJ L 248, 18.9.2013, p. 1).

58 Interinstitutional Agreement of 25 May 1999 between the European Parliament, the Council of the European Union and the Commission of the European Communities concerning internal investigations by the European Anti-fraud Office (OLAF) (OJ L 136, 31.5.1999, p. 15).

4. OLAF may carry out investigations, including on-the-spot checks and inspections with a view to establishing whether there has been fraud, corruption or any other illegal activity affecting the financial interests of the Union in connection with a grant or a contract funded by the Agency, in accordance with the provisions and procedures laid down in Regulation (EU, Euratom) No 883/2013 and Council Regulation (Euratom, EC) No 2185/96[59].

5. Working agreements with third countries and international organisations, contracts, grant agreements and grant decisions of the Agency shall contain provisions expressly empowering the European Court of Auditors and OLAF to conduct such audits and investigations, according to their respective competences.

6. In accordance with Council Regulation (EU) 2017/1939[60], the EPPO may investigate and prosecute fraud and other illegal activities affecting the financial interests of the Union as provided for in Directive (EU) 2017/1371 of the European Parliament and of the Council[61].

Section 4
General provisions governing the Agency

Article 157
Liability

1. The contractual liability of the Agency shall be governed by the law applicable to the contract in question. The Court of Justice of the European Union shall have jurisdiction pursuant to any arbitration clause contained in a contract concluded by the Agency.

2. In the case of non-contractual liability, the Agency shall, in accordance with the general principles common to the laws of the Member States, make good any damage caused by it or by its staff in the performance of their duties.

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59 Council Regulation (Euratom, EC) No 2185/96 of 11 November 1996 concerning on-the-spot checks and inspections carried out by the Commission in order to protect the European Communities' financial interests against fraud and other irregularities (OJ L 292, 15.11.1996, p. 2).

60 Council Regulation (EU) 2017/1939 of 12 October 2017 implementing enhanced cooperation on the establishment of the European Public Prosecutor's Office ('the EPPO') (OJ L 283, 31.10.2017, p. 1).

61 Directive (EU) 2017/1371 of the European Parliament and of the Council of 5 July 2017 on the fight against fraud to the Union's financial interests by means of criminal law (OJ L 198, 28.7.2017, p. 29).

The Court of Justice shall have jurisdiction in any dispute relating to compensation for any such damage.

3. The personal liability of its staff towards the Agency shall be governed by the provisions laid down in the Staff Regulations or Conditions of Employment of Other Servants applicable to them.

Article 158
Access to documents

Regulation (EC) No 1049/2001 shall apply to documents held by the Agency.

The Agency shall set up a register pursuant to Article 2(4) of Regulation (EC) No 1049/2001 to make available all documents that are publicly available pursuant to this Regulation.

The Management Board shall adopt the arrangements for implementing Regulation (EC) No 1049/2001.

Decisions taken by the Agency pursuant to Article 8 of Regulation (EC) No 1049/2001 may give rise to the lodging of a complaint with the Ombudsman or form the subject of an action before the Court of Justice, under the conditions laid down in Article 228 and Article 263 of the Treaty respectively.

Article 159
Privileges

Protocol No 7 on the Privileges and Immunities of the European Union annexed to the Treaty on the Functioning of the European Union shall apply to the Agency and its staff.

Article 160

Staff

The Staff Regulations and the rules adopted by agreement between the institutions of the Union for giving effect to those Staff Regulations and Conditions of Employment of Other Servants shall apply to the staff of the Agency.

The Agency may make use of seconded national experts or other staff not employed by the Agency. The Management Board, in agreement with the Commission, shall adopt the necessary implementing provisions.

Article 161

Security rules on the protection of classified and sensitive non-classified information

The Agency shall adopt own security rules equivalent to the Commission's security rules for protecting European Union Classified Information (EUCI) and sensitive non-classified information, as set out in Commission Decisions (EU, Euratom) 2015/443[62] and 2015/444[63]. The security rules of the Agency shall cover, inter alia, provisions for the exchange, processing and storage of such information.

Members of the Management Board, the Executive Director, members of the committees, external experts participating in ad hoc working groups, and members of the staff of the Agency shall comply with the confidentiality requirements under Article 339 TFEU, even after their duties have ceased.

[62] Commission Decision (EU, Euratom) 2015/443 of 13 March 2015 on Security in the Commission (OJ L 72, 17.3.2015, p. 41).

[63] Commission Decision (EU, Euratom) 2015/444 of 13 March 2015 on the security rules for protecting EU classified information (OJ L 72, 17.3.2015, p. 53).

The Agency may take the necessary measures to facilitate the exchange of information relevant to its tasks with the Commission and the Member States and, where appropriate, the relevant Union institutions, bodies, offices and agencies. Any administrative arrangements concluded to that end with regard to the sharing of EU classified information (EUCI) or, in the absence of such arrangements, any exceptional ad hoc release of EUCI, shall have received the Commission's prior approval.

Article 162

Consultation process

1. The Agency shall establish a consultation process with relevant national authorities or bodies for the exchange of information and pooling of knowledge on general issues of scientific or technical nature related to the tasks of the Agency, in particular guidelines on unmet medical needs and the design of clinical trials, other studies and the generation of evidence along the life cycle of medicinal products.

   The consultation process shall include bodies responsible for health technology assessment as referred to in Regulation (EU) 2021/2282 and national bodies responsible for pricing and reimbursement.

   The conditions of participation shall be set by the Management Board in agreement with the Commission.

2. The Agency may extend the consultation process to patients, medicine developers, healthcare professionals, industries or other stakeholders, as relevant.

Article 163

Contacts with civil society representatives

The Management Board shall, in agreement with the Commission, develop appropriate contacts between the Agency and the representatives of the industry, consumers and patients and the healthcare professions. These contacts may include the participation of observers in certain aspects of the Agency's work, under conditions determined beforehand by the Management Board, in agreement with the Commission.

Article 164

Support to SMEs and to not-for profit entities

1. The Agency shall ensure that micro, small and medium-sized enterprises ('SMEs') and not-for-profit entities are offered a support scheme.

2. The support scheme shall be comprised of regulatory, procedural and administrative support and reduction, deferral or waivers of fees.

3. The scheme shall cover the various steps involved in pre-authorisation procedures, and in particular scientific advice, the submission of the marketing authorisation application, and the post-authorisation procedures.

4. SMEs shall benefit from the incentives laid down in Commission Regulation (EC) No 2049/2005 and [revised Council Regulation (EC) No 297/95][64].

5. For not-for-profit entities, the Commission shall adopt specific provisions clarifying the definitions, establishing waivers, reductions or deferrals of fees, as appropriate, in accordance with the procedure referred to in Article 10 and Article 12 of [revised Regulation (EC) No 297/95].

[64] Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products (OJ L 35, 15.2.1995, p. 1).

Article 165

Transparency

To ensure an appropriate level of transparency, the Management Board shall, on the basis of a proposal by the Executive Director and in agreement with the Commission, adopt rules to ensure the availability to the public of regulatory, scientific or technical information concerning the authorisation or supervision of medicinal products for human use which is not of a confidential nature.

The internal rules and procedures of the Agency, its committees and its working groups shall be made available to the public at the Agency and on the Internet.

The Agency may engage in communication activities on its own initiative within its field of competence. The allocation of resources to communication activities shall not be detrimental to the effective exercise of the tasks of the Agency. Communication activities shall be carried out in accordance with relevant communication and dissemination plans adopted by the Management Board.

Article 166

Personal health data

1. To support its public health tasks and in particular the evaluation and monitoring medicinal products or the preparation of regulatory decisions and scientific opinions, the Agency may process personal health data, ~~from sources other than clinical trials,~~ for the purpose of improving the robustness of its scientific assessment or verifying claims of the applicant or marketing authorisation holder in the context of the evaluation or supervision of medicinal product.

~~2. The Agency~~**~~, through its scientific committees,~~** ~~may consider and decide upon additional evidence available, independently from the data submitted by the marketing authorisation applicant or marketing authorisation holder. On that basis, the summary of product characteristics shall be updated if the additional evidence has an impact on the benefit-risk balance of a medicinal product.~~

3. The Agency shall adopt adequate data governance practices and the required standards to ensure the appropriate use and protection of personal health data, in accordance with this Regulation and Regulation (EU) 2018/1725.

Article 167

Protection against cyber attacks

The Agency shall equip itself with a high level of security controls and processes against cyber attacks, cyber espionage and other data breaches to ensure the protection of health data and the normal functioning of the Agency at all times, especially during public health emergencies or major events at Union level.

For the purposes of the first subparagraph, the Agency shall actively identify and implement cybersecurity best practices adopted within Union institutions, bodies, offices and agencies for preventing, detecting, mitigating, and responding to cyber attacks.

Article 168

Confidentiality

1. Unless otherwise provided for in this Regulation and without prejudice to Regulation (EC) No 1049/2001 and Directive (EU) 2019/1937 of the European Parliament and of the Council[65], and existing national provisions and practices in the Member States on confidentiality, all parties involved in the application of this Regulation shall respect the confidentiality of information and data obtained in carrying out their tasks in order to protect the commercially confidential information and trade secrets of natural or legal persons in accordance with Directive (EU) 2016/943 of the European Parliament and of the Council[66], including intellectual property rights.

[65] Directive (EU) 2019/1937 of the European Parliament and of the Council of 23 October 2019 on the protection of persons who report breaches of Union law (OJ L 305, 26.11.2019, p. 17).

[66] Directive (EU) 2016/943 of the European Parliament and of the Council of 8 June 2016 on the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure (OJ L 157, 15.6.2016, p. 1).

2. Without prejudice to paragraph 1, all parties involved in the application of this Regulation shall ensure that no commercially confidential information is shared in a way which has the potential to enable undertakings to restrict or distort competition within the meaning of Article 101 TFEU.

3. Without prejudice to paragraph 1, information exchanged on a confidential basis between competent authorities of the Member States and between competent authorities of the Member States and the Commission and the Agency shall not be disclosed without the prior agreement of the authority from which that information originates.

4. Paragraphs 1, 2 and 3 do not affect the rights and obligations of the Commission, the Agency, Member States or other actors identified in this Regulation with regard to the exchange of information and the dissemination of warnings, nor do they affect the obligations of the persons concerned to provide information under criminal law.

5. The Commission, the Agency, and Member States may exchange commercially confidential information with regulatory authorities of third countries with which they have concluded bilateral or multilateral confidentiality arrangements.

Article 169

Processing of personal data

1. The Agency may process personal data, including personal health data, for the performance of its tasks as referred to in Article ~~135~~ **138**, in particular for the purpose of improving the robustness of its scientific assessment or verifying claims of the applicant or marketing authorisation holder in the context of the evaluation or supervision of medicinal products.

   Additionally, the Agency may process such data for the performance of regulatory science activities, as defined in paragraph 2, provided that the processing of those personal data:

   (a) is strictly required and duly justified to achieve the objectives of the project or of the horizon scanning activities concerned;

   (b) as regards special categories of personal data, is strictly necessary and subject to appropriate safeguards, which may include pseudonymisation.

2. For the purpose of this Article, ‘regulatory science activities’ shall mean scientific projects to complement available scientific evidence with regard to diseases or horizontal questions related to medicinal products, to fill evidence gaps that cannot be fully addressed through data in the possession of the Agency, or to support horizon scanning activities.

3. The processing of personal data by the Agency in the context of this Article shall be guided by the principles of transparency, explainability, fairness, and accountability.

4. The Management Board shall establish the general scope for the regulatory science activities in consultation with the Commission and the European Data Protection Supervisor.

5. The Agency shall keep documentation containing a detailed description of the process and of the rationale behind the training, testing and validation of algorithms to ensure transparency of the process and the algorithms, including their compliance with the safeguards provided for in this Article, and to allow for verification of the accuracy of the results based on the use of such algorithms. Upon request, the Agency shall make relevant documentation available to interested parties, including Member States.

6. If the personal data to be processed for the regulatory science activities have been directly provided by a Member State, a Union body, a third country or an international organisation, the Agency shall request authorisation from that provider of data, unless the provider of data has granted its prior authorisation to such processing for the purpose of regulatory science activities, either in general terms or subject to specific conditions.

7. Processing of personal data under this Regulation shall be subject to Regulations (EU) 2016/679 and (EU) 2018/1725, as applicable.

Article 170

Evaluation

1. Not later than [*note to OP = five years after the date of entry into application*], and every 10 years thereafter, the Commission shall commission an evaluation of the Agency's performance in relation to its objectives, mandate, tasks, governance and location(s) in accordance with Commission's guidelines. **The evaluation shall include, amongst others, based on the reports referred to in Articles 144 point q and qa, a quantitative assessment of the efficiency gain, the appropriate involvement of scientific expertise in particular regarding orphan, paediatric medicinal products and ATMPs as well as the broad geographical representation of national experts in the work of the scientific committees, advisory groups and working parties.**

2. The evaluation shall, in particular, address the possible need to modify the mandate of the Agency, and the financial implications of any such modification.

3. On the occasion of every second evaluation, there shall be an assessment of the results achieved by the Agency having regard to its objectives, mandate, governance and tasks, including an assessment of whether the continuation of the Agency is still justified with regard to these objectives, mandate, governance and tasks. This assessment shall also include the experience acquired as a result of the operation of the procedures laid down in this Regulation and in Chapter III, Sections 4 and 5 of [revised Directive 2001/83/EC] on the basis of input from Member States and the Coordination group referred to in Article 37 of [revised Directive 2001/83/EC].

4. The Commission shall report to the European Parliament, the Council and the Management Board on the evaluation findings. The findings of the evaluation shall be made public.

5. By 10 years following the entering into application, the Commission shall assess the application of this Regulation and produce an evaluation report on the progress towards achievement of the objectives contained herein including an assessment of the resources required to implement this Regulation.

CHAPTER XIV

AMENDMENTS TO OTHER LEGAL ACTS

Article 176

Amendments to Regulation (EC) No 1394/2007

Regulation (EC) No 1394/2007 is amended as follows:

(1) Articles 8, 17 and 20 to 23 are deleted;

(2) in Article 9(3), the fourth subparagraph is replaced by the following:

'If the application does not include the results of the assessment, the Agency shall seek an opinion on the conformity of the device part with Annex I to Regulation (EU) 2017/745 of the European Parliament and of the Council* from a notified body identified in conjunction with the applicant, unless the Committee for Medicinal Products for Human Use advised by its experts for medical devices decides that involvement of a notified body is not required.

*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).'

Article 178

Amendments to Regulation (EU) 2022/123

Regulation (EU) No 2022/123 is amended as follows:

1. In Article 18, the following paragraph (7) is added:

   '(7) Where a request has been made in accordance with Article 18(3) of Regulation (EU) 2022/123 and there is an application for a temporary emergency marketing authorisation for the medicinal product concerned in accordance with Article 30 of Regulation [Note to OP: Please fill in with the number of this Regulation]*, the procedure initiated under that Regulation shall prevail.'

   * [OP: Insert the full title of that Regulation and the OJ reference, please]

2. Articles 33 and 34 are deleted.

6TH READING PACKAGE

PROCEDURES FOR NATIONAL MARKETING AUTHORISATIONS

RECITALS

REVISED DIRECTIVE

(10) The system of a directive and regulation for the general pharmaceutical legislation should be maintained to avoid fragmentation of national legislation on medicinal products for human use, given that the legislation is based on a system of national Member States and Union marketing authorisations. Member States national marketing authorisations are granted and managed on the basis of national law implementing the Union pharmaceutical law. The evaluation of the general pharmaceutical legislation has not shown that the choice of legal instrument has caused specific problems or created disharmonisation. In addition, a REFIT Platform2 opinion in 2019 showed that there was not support among the Member States to turn Directive 2001/83/EC into a Regulation.

(13) To avoid the duplication of requirements for medicinal products in this Directive and in the Regulation, the general standards in regards to quality, safety and efficacy of medicinal products laid down in this Directive shall be applicable to medicinal products covered by national marketing authorisation and also to medicinal products covered by centralised marketing authorisation. Therefore, the requirements for an application for medicinal product are valid for both, also the rules on prescription status, product information, regulatory protection and rules on manufacturing, supply, advertising, supervision and other national requirements shall be applicable to medicinal products covered by centralised marketing authorisation.

(25) In order to ensure that the data supporting the marketing authorisation concerning the use of a product in children to be authorised under this regulation have been correctly developed, the competent authorities should check compliance with the agreed paediatric investigation plan and any waivers and deferrals at the validation step for marketing authorisation applications.

(34) 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. The legislation should allow under similar circumstances for medicinal products with a standard marketing authorisation for new therapeutic indications to be authorised on a conditional basis or under exceptional circumstances. The 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 shall be subject to specific review of the fulfilment of the imposed specific conditions or obligations. The grounds for refusal of a marketing authorisation should apply mutatis mutandis for such cases.

(35) With the exception of those medicinal products that are subject to the centralised authorisation procedure established by [revised Regulation (EU) No. 726/2004], 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 applicants and competent authorities, a full in-depth assessment of an application for the authorisation of a medicinal product should be carried out only once. It is appropriate therefore to lay down special procedures for the mutual recognition of national authorisations. Moreover, it should be possible to submit **through decentralised procedure** the same application in parallel in several Member States for the purpose of a common assessment under the lead of one of the Member States concerned.

(36) Moreover, rules should be established under those procedures to resolve any disagreements between competent authorities in a coordination group for mutual recognition and decentralised procedures medicinal products ('the coordination group') 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 evaluation of the matter should be undertaken according to a Union standard, leading to a single decision on the area of disagreement binding on the Member States concerned. Whereas this decision should be adopted by a rapid procedure ensuring close cooperation between the Commission and the Member States.

(37) In certain cases of major disagreement that cannot be solved, the case should be escalated and be subject to a scientific opinion of the Agency, which is then implemented through a Commission Decision.

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

(39) In the interest of as broad as possible access to medicinal products, a Member State that has an interest in receiving access to a particular medicinal product undergoing authorisation through the decentralised and mutual recognition procedures should be able to opt-into that procedure.

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

(41) In the case of generic medicinal products of which the reference medicinal product has been granted a marketing authorisation under the centralised procedure, applicants seeking marketing authorisation should be able to choose either of the two procedures, on certain conditions. Similarly, the mutual-recognition or decentralised 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 medicines 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, therefore, the procedures to include other Member States concerned to such procedure should be further simplified.

(42) 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 and therefore, the scientific evaluation period should remain. ~~However, the reduction of overall period for marketing authorisation procedure from 210 days to 180 days is foreseen.~~

(65) The competent authorities should refuse the validation for an application for a marketing authorisation 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 the marketing authorisation. The competent authorities cannot base their decision on any other grounds. In particular, those decisions cannot be based on the patent or SPC status of the reference medicinal product.

(79) As a general rule, risk management plans for generic and biosimilar medicinal products should not be developed and submitted, considering that the reference medicinal product has such a plan, except in specific cases, where a risk management plan should be provided. Furthermore, as a general rule a marketing authorisation should be granted for an unlimited period; exceptionally, one renewal may be decided only on justified grounds related to the safety of the medicinal product.

(142) 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 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. In order to ensure that the data supporting the marketing authorisation concerning the use of a product in children, the competent authorities responsible for the authorisation of a medicinal product should check compliance with the agreed paediatric investigation plan and any waivers and deferrals at the validation step for marketing authorisation applications.

(143) 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, independently from the fact that they support or not the use of the medicinal product in children, appropriate information should be included in the summary of product characteristics and, if appropriate, in the package leaflet. Information on waivers should also be included in product information. When all the measures 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.

Chapter III

Procedures for national marketing authorisations

Section 1

General provisions

Article 29

Examination of marketing authorisation application

1. In order to examine an application submitted in accordance with Articles 6 and 9 to 14, the competent authority of the Member State:
   (a) shall verify whether the particulars and documentations submitted in support of the application comply with Articles 6 and 9 to 14 ('validation'), and examine whether the conditions for issuing a marketing authorisation set out in Articles 43 to 45 are complied with;
   (b) may submit the medicinal product, its starting materials or ingredients and, if need be, its intermediate products or other **constituents** ~~**materials**~~, for 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 application in accordance with Annex I are satisfactory;
   (c) may, where appropriate, require the applicant to supplement the particulars accompanying the application in respect of the items listed in the Articles 6 and 9 to 14;
   (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 **and to require changes in the summary of product characteristics**.
   (e) may, where appropriate, require the applicant to provide ~~**supportive**~~ **raw data concerning the pharmaceutical and non-clinical tests and the clinical studies referred to in Annex I**

~~2. Where the competent authority of the Member State avails itself of the option referred to in the first subparagraph, point (c), the time limits laid down in Article 30 shall be suspended until such time as the supplementary information required has been provided or for the time allowed to the applicant for giving oral or written explanations.~~

3. Where**, in the course of the validation referred to in paragraph 1, point (a),** the competent authority of the Member State considers that the marketing authorisation application is incomplete, or contains ~~critical~~ deficiencies **to the extent** ~~-~~that **this** may prevent the evaluation of the ~~medicinal product~~ **application,** it shall inform the applicant accordingly and shall set a time limit for submitting the missing information and documentation. If the applicant fails to provide the missing information and documentation within the time limit set, the application shall be considered to have been withdrawn.

3a. Where the competent authority of the Member State avails itself of the option referred to in ~~the first subparagraph~~ **paragraph 1**, point (c), the time limits laid down in Article 30 shall be suspended until such time as the supplementary information required has been provided or for the time allowed to the applicant for giving ~~oral or written~~ explanations.

4. In cases where on examination of an application for a marketing authorisation the competent authority of the Member State considers that the submitted data are not of sufficient quality or maturity for the completion of the examination of the application, the examination can be terminated within 90 days of the **date of** validation of the application.

Prior to the termination, t~~T~~he 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 applicant accordingly and set a time limit to address the deficiencies. The application shall be suspended until the applicant addresses the deficiencies. If the 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** application shall be considered as withdrawn.

5. ~~In case of a potential serious risk to public health with regards to a reference medicinal product, Member States shall suspend the examination of marketing authorisation applications submitted under Articles 9 to12 that refer to that reference medicinal product, until the end of the procedure initiated under Article 39.~~

In case a suspension or revocation of the marketing authorisation of ~~potential serious risk to public health related to~~ the reference medicinal product is examined under a specific procedure under this Directive or [revised Regulation (EC) No 726/2004], the Member States shall suspend the examination of any marketing authorisation application submitted under Articles 9 to 12 that uses the same reference medicinal product until the end of the procedure related to the reference medicinal product.

6. **Where a competent authority of the Member State ~~notes is informed~~ becomes aware that another marketing authorisation application for the same medicinal product is being examined by a competent authority of another Member State, ~~the competent authority of the Member States concerned~~ it shall ~~decline~~ refuse to ~~examine~~ validate the application and advise the applicant to use the procedure referred to in Articles 34 or 36.**

7. **Where the competent authorities of the Member States ~~are informed~~ become aware that another Member State has authorised ~~a~~ the same medicinal product ~~that is the subject of a marketing authorisation application in the Member State concerned~~, they shall ~~reject~~ refuse to validate the application unless it was submitted in compliance with the provisions referred to in Articles 34 or 36.**

Article 30

Duration of examination of 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 a maximum of ~~180~~ **210** days after the submission of a valid application from the date of validation of a marketing authorisation application.

Commented [A7]: SI proposes amendment since the wording should be clearer (less ambigous).
We suggest to avoid the terminology "potential serious risk to public health" when referring to a reference product holding a valid MA, since this terminology is used only when referring to medicines being assessed in ongoing procedures (see Art 38, divergent positions of MS). It would not be correct to use this terminology for a European MP that already holds a MA in an EU country. The proposal would also increase the already huge workload for NCAs, which will be faced with additional assessment (during the refferals) of already assessed and approved dossiers for medicines. MAHs are already obliged to follow scientific and technical progress through whole lifecycle of medicinal product by default which ensures the medicinal products on the market are in accordance with the Acqui.
We should bear in mind the principle of the mutual recognition of decisions of MS which demands that MSs trust each other's assessments and competency. Furthermore, we should not forget that requirements for evaluation of pharmaceutical products have been changing substantially over last decades.

Commented [A8]: SI: A clear definition of "the same medicinal product" should be included in the proposed Directive (or Recital).

It is suggested to use the definition from the Commission Communication on the Community marketing authorisation procedures for medicinal products (OJ C 229, 22.7.1998, p. 4-17) (98/C 229/03) .

Article 31

Types of national marketing authorisation procedures

National marketing authorisations may be granted in accordance with the procedures laid down in Article 32 ('purely national marketing authorisation procedure'), Articles 33 and 34 ('decentralised procedure for national marketing authorisation') or Articles 35 and 36 ('mutual recognition procedure for national marketing authorisation').

Section 2

Marketing authorisations valid in a single Member State

Article 32

Purely national marketing authorisation procedure

1. An application for marketing authorisation ~~according to Article 6(2)~~ under the purely national marketing authorisation procedure shall be submitted to the competent authority in that Member State in which the marketing authorisation is applied.

2. The competent authority in the Member State concerned shall examine the application in accordance with Articles 29 and 30**, ~~draw up~~ prepare an assessment report** and grant a marketing authorisation in accordance with Articles 43 to 45 and applicable national provisions.

3. A marketing authorisation granted under the purely national marketing authorisation 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 33

Scope of decentralised procedure for national marketing authorisations

1. ~~**In cases where the medicinal product has not been granted a marketing authorisation at the time of application, a**~~An application for marketing authorisation under the decentralised procedure for national marketing authorisation in several Member States in respect of the same medicinal product shall be submitted to the competent authorities in those Member States in which the marketing authorisation is applied.

2. The competent authorities in the Member State concerned shall examine the applications in accordance with Articles 29, 30 and 34 and grant a marketing authorisation in accordance with Articles 43 to 45.

~~3. Where a competent authority of the Member State notes that another marketing authorisation application for the same medicinal product is being examined by the competent authority in another Member State, the competent authorities of the Member States concerned shall decline to examine the application and shall advise the applicant that the provisions referred to in Articles 35 and 36 apply.~~

~~4. Where the competent authorities of the Member States are informed that another Member State has authorised a medicinal product that is the subject of a marketing authorisation application in the Member State concerned, they shall reject the application unless it was submitted in compliance with the provisions referred to in Articles 35 and 36.~~

5. Marketing authorisations granted under **the** decentralised procedure for national marketing authorisation shall be valid only in those Member States of the competent authorit**ies**~~y~~ that granted ~~it~~ ~~**such**~~ **the authorisations**.

Article 34

Decentralised procedure for national marketing authorisations

1. With a view to obtain a national marketing authorisation for a medicinal product in several Member States in respect of the same medicinal product under the decentralised procedure for national marketing authorisation, an applicant shall submit a marketing authorisation application based on an identical dossier to the competent authority of the Member State chosen by the applicant, to prepare an assessment report on the medicinal product in accordance with Article 43(5) and to act in accordance with this Section ('reference Member State for the decentralised procedure'), and to the competent authorities in the other Member States concerned.

2. The application for marketing authorisation shall contain:
   (a) the particulars and documentations referred to **in** Articles 6, 9 to 14 ~~and 62~~ **and 62**;
   (b) a list of Member States concerned by the application.

3. The applicant shall inform all the competent authorities of all Member States of its application at the time of submission. **If necessary to meet the needs of patients in that Member State,** ~~T~~**t**he competent authority of a Member State may request ~~for justified public health reasons~~ to enter the procedure and shall inform the applicant and the competent authority of the reference Member State for the decentralised procedure of its request within 30 days from the date of submission ~~**validation**~~ of the application. The applicant shall provide the competent authorities of those Member States entering the procedure with the application without undue delay. **The Member State that requests to enter the decentralised procedure under this paragraph shall be considered as Member State concerned.**

3a. **Where, in the course of the validation referred to in Article 29, paragraph 1, point (a), the competent authority of the reference Member State for the decentralised procedure considers that the information in the submitted marketing authorisation application is incomplete or contains deficiencies to the extent that this may prevent the evaluation of the application ~~not of sufficient quality or maturity for the completion of the examination~~, it shall inform the applicant accordingly and shall set a time limit for submitting the missing information and documentation. If the applicant fails to provide the missing information and documentation within the time limit set, the application shall be considered to have been withdrawn.**

4. In cases where on examination of an application for a marketing authorisation the competent authority of the reference Member State for the decentralised procedure considers that the submitted data are not of sufficient quality or maturity for the completion of the examination of the application, the examination can be terminated within ~~90~~ **70** days of **the ~~completion~~ date of** the validation of the application.

Prior to the termination, ~~T~~**t**he 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 applicant and the competent authorities of the Member States concerned accordingly and set a time limit to address the deficiencies. The application shall be suspended until the applicant addresses the deficiencies. If the applicant fails to address those deficiencies within the time limit set by the competent authority of the reference Member State for the decentralised procedure, the **assessment shall be terminated and the** application shall be considered as withdrawn **by the applicant**.

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

5. Within 120 days after **the ~~completion~~ date of the** validation of the application, the competent authority of the reference Member State for the decentralised procedure shall prepare an assessment report, a summary of product characteristics, the labelling and the package leaflet and shall send them to the Member States concerned and to the applicant.

Commented [A9]: SI: "Start of the procedure" would be more in line with the current practice than "date of validation" since validation dates differ between MSs involved in the procedure and the procedure is started by the RMS once all the MSs have validated the application.

6. Within ~~60~~ **90** days of receipt of the assessment report, the competent authorities of the Member States concerned shall approve the assessment report, the summary of product characteristics and the labelling and 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 record the agreement of all parties, close the procedure and inform the applicant accordingly.

6a. Within 7 days of the receipt of the information under paragraph 6 the applicant shall submit the high quality translations of the summary of product characteristics, the labelling and the package leaflet to the each of the competent authorities concerned.

7. Within 30 **~~23~~** days after ~~acknowledgement of the agreement~~ **~~and~~ receipt of the translations ~~of the summary of product characteristics, the labelling and the package leaflet from the applicant~~referred to in paragraph 6a**, the competent authorities of all Member States concerned in which an application has been submitted in accordance with paragraph 1 shall adopt a decision according to Articles 43 to 45 and in conformity with the approved assessment report, the summary of product characteristics and the labelling and package leaflet as approved.

Section 4

Mutual recognition of national marketing authorisations

Article 35

*Scope of mutual recognition procedure for national marketing authorisation**s***

1. **Where the medicinal product has already received a marketing authorisation in accordance with Articles 43 to 45 at the time of application, it shall be recognised in other Member States in accordance with the procedure laid down in Article 36.**

2. An application for marketing authorisation for mutual recognition procedure for national marketing authorisation, granted under Articles 43 to 45 ~~and in accordance with Article 32~~, shall be submitted to the competent authorities of other Member States in accordance with the procedure laid down in Article 36.

Article 36

Mutual recognition procedure for national marketing authorisations

1. An application for mutual recognition of a marketing authorisation, granted under Articles 43 to 45 ~~and in accordance with Article 32~~, in several Member States in respect of the same medicinal product shall be submitted to the competent authority of **one of** the Member State**s** that granted ~~the~~ **a** marketing authorisation ('reference Member State for the mutual recognition procedure') and to the competent authorities of the Member States concerned where the applicant seeks to obtain a national marketing authorisation.

2. Application shall include a list of Member States concerned by the application.

3. The competent authority of the reference Member State for the mutual recognition procedure ~~shall~~ may ~~reject~~ **refuse the request** ~~**validation and assessment of**~~ ~~an application~~ for mutual recognition of marketing authorisation of medicinal product within a year ~~**six months**~~ from the granting of that marketing authorisation, unless the competent authority of the Member State informs the competent authority of the reference Member State for the mutual recognition procedure of its interest in this medicinal product.

Commented [A10]: SI would strongly suggest that "shall" in the first sentence is changed to "may".

4. The applicant shall inform the competent authorities of all Member States of its application at the time of submission **referred to in paragraph 1**. **If necessary to meet the needs of patients in that Member State,** ~~T~~the competent authority of a Member State may request ~~for justified public health reasons~~ to enter the procedure and shall inform the applicant and the competent authority of the reference Member State for the mutual recognition procedure of its request within 30 days from the date of submission ~~**validation**~~ of the application. The applicant shall provide the competent authorities of those Member States entering the procedure with the application without undue delay.

5. ~~If **any of** the competent authorities of the Member States concerned so require, the marketing authorisation holder shall request the competent authority of the reference Member State for the mutual recognition procedure to update the assessment report drawn on the medicinal concerned by the application. In that case, the reference Member State shall update the assessment report within 90 days after **the completion date of the** validation of the application. If **none of** the competent authorities of the Member States concerned do not require the update of the assessment report, the reference Member State shall provide the assessment report within 30 days **after the completion date of the validation of the application** .~~ **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 concerned Member States and to the applicant** ~~**within 90 days after**~~ **before the date of validation of the application.**

Commented [A11]: **RED LINE:**
SI proposes following change.
Rationale:
According to the curent proposal and paragraph 6 of this article the timeline for the procedure could be understood to be up to 180 days which is not in line for MRP procedures.

6. Within ~~60~~ **90** days of receipt of the assessment report, the competent authorities of the Member States concerned shall approve the assessment report, the summary of product characteristics, the labelling and package leaflet and shall inform the competent authority of the reference Member State accordingly.

7. The competent authority of reference Member State for the mutual recognition procedure shall record the agreement of all parties, close the procedure and inform the applicant accordingly. ~~The assessment report together with the summary of product characteristics, labelling and package leaflet approved by the competent authority of the reference Member State for the mutual recognition procedure shall be sent to the Member States concerned and to the applicant.~~

7a. Within 7 days of the receipt of the information under paragrpaph 7 the applicant shall submit the high quality translations of the the summary of product characteristics, the labelling and the package leaflet to the each of the competent authorities concerned.

8. Within 30 ~~23~~ days after ~~acknowledgement of the agreement~~ **and the receipt of the ~~high quality translations of the summary of product characteristics, the labelling and the package leaflet from the applicant~~ translations referred to in paragraph 7a**, the competent authorities of all Member States concerned in which an application has been submitted in accordance with paragraph 1 shall adopt a decision according to Articles 43 to 45 in conformity with the approved assessment report, the summary of product characteristics, the labelling and package leaflet as approved.

Section 5

Coordination of national marketing authorisation

Article 37

Coordination group for decentralised and mutual recognition procedures

1. A coordination group for decentralised and mutual recognition procedures ('coordination group') shall be set up for the following purposes:
   (a) the examination of any question relating to a national marketing authorisation of a medicinal product in two or more Member States in accordance with the procedures laid down in Sections 3, 4 and 5 of this Chapter, and Article 95;
   (b) the examination of questions related to the pharmacovigilance of medicinal products covered by national marketing authorisations, in accordance with Articles 108, 110, 112, 116 and 121;
   (c) the examination of questions relating to variations of national marketing authorisations, in accordance with Article 93(1)
   (d) the establishment and publication of a list of medicinal products for which a harmonised summary of product characteristics is to be drawn up, in accordance with Article 40.

   For the fulfilment of its pharmacovigilance tasks contemplated under first subparagraph, point (b), including approving risk management systems and monitoring their effectiveness, the coordination group shall rely on the scientific assessment and the recommendations of the Pharmacoigilance Risk Assessment Committee referred to in Article 149 of [revised Regulation (EC) No 726/2004].

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.

Members of the coordination group and experts shall, for the fulfilment of their tasks, 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 nominated coordination group members and experts.

Article 147 of [revised Regulation (EC) No 726/2004] shall apply to the coordination group as regards transparency and the independence of its members.

3. The Agency shall provide the secretariat of this 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. These 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 the marketing authorisation.

6. Where 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 38

Divergent positions of Member States in decentralised or mutual recognition procedure

1. If, at the end of the period laid down in Articles 34(6) or 36(6), there is disagreement between Member States on whether the marketing authorisation can be issued, on the grounds of potential serious risk to public health, the ~~disagreeing~~ Member State**s** concerned shall give a detailed explanation of the points of disagreement and the reasons for its position to the reference Member State, to the other 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, ~~all disagreeing~~ Member States ~~concerned~~ shall use their best endeavours to reach agreement on the action to be taken. They shall allow the applicant the 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 record the agreement, close the procedure and inform the applicant accordingly. The procedure laid down in Articles 34(7) or 36(8) shall apply.

4. If within the 60-day period laid down in paragraph 3, 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 the Commission to refer the matter to the CHMP.**

~~which~~ **The Commission** shall apply the procedure laid down in Article~~s 41 and~~ 42. **Where the Commission on its own initiative or based on the recommendation of the coordination group considers that the matter shall be referred to the Committee for Medicinal Products for Human Use, Article 41 shall also apply.**

5. In the circumstances referred to in paragraph 4, Member States that have approved the assessment report, the summary of product characteristics, the labelling and 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 4~~1~~**2**. In that event, the national marketing authorisation granted shall be without prejudice to the outcome of that procedure.

Article 39

Referral procedure of divergent decisions of Member States

If applications for a national marketing authorisation have been submitted in accordance with Articles 6 and 9 to 14 for a particular medicinal product, and if 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, the Commission ~~or the marketing authorisation holder~~ may refer the matter to the Committee for Medicinal Products for Human Use for the application of the procedure laid down in Articles 41 and 42.

Article 40

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 ~~shall~~**may**, each year, forward to the coordination group referred to in Article 37 a list of medicinal products for which a harmonised summary of product characteristics is to be drawn up.

2. The coordination group ~~shall~~ **may** lay down 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 forward that list to the Commission.

3. The Commission or the competent authority of a Member State, in agreement with the Agency and taking into account the views of interested parties, may refer the matter concerning the harmonisation of summary of products characteristics of those medicinal products to the ~~Committee for Medicinal Products for Human Use for the application of the procedure laid down in Articles 41 and 42~~ **coordination group**.

Article 41

Scientific evaluation by the Committee for Medicinal Products for Human Use in a referral procedure

1. When reference is made to the procedure laid down in this Article, the Committee for Medicinal Products for Human Use referred to in Article 148 of [revised Regulation (EC) No 726/2004] shall consider the matter concerned and shall issue a reasoned opinion within 60 days from the date when the matter was referred to it.

   However, in cases submitted to the Committee for Medicinal Products for Human Use in accordance with Articles 39~~, 40~~ and 95, this period 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.

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 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 these tasks.

3. Before issuing its opinion, the Committee for Medicinal Products for Human Use shall provide the 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 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 before it or consider a public hearing.

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 163 of [revised Regulation (EC) No 726/2004].

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

4. The Agency shall without undue delay inform the applicant or the marketing authorisation holder where the opinion of the Committee for Medicinal Products for Human Use provides that:
   (a) the application does not satisfy the criteria for a marketing authorisation;
   (b) the summary of product characteristics proposed by the applicant or the marketing authorisation holder in accordance with Article 62 is to be amended;
   (c) the 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 marketing authorisation is to be suspended, varied or revoked;
   (e) the medicinal product satisfies the conditions set out in Article 83 regarding medicinal products addressing an unmet medical need.

   Within 12 days after receipt of the opinion, the applicant or the marketing authorisation holder may notify the Agency in writing of its intention to request a re-examination of the opinion. In that case, they shall forward to the Agency the detailed grounds for the request within 60 days after receipt of the opinion.

Within 60 days following receipt of the grounds for the request, the Committee for Medicinal Products for Human Use shall re-examine its opinion in accordance with Article 12(2), third subparagraph, of [revised Regulation (EC) No 726/2004]. The reasons for the conclusion reached further to its re-examination shall be annexed to the assessment report referred to in Article 12(2), third subparagraph, of [revised Regulation (EC) No 726/2004].

5. Within 12 days after its adoption, the Agency shall forward the final opinion of the Committee for Medicinal Products for Human Use to the competent authorities of the Member States, to the Commission and to the 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 62;

(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 package leaflet.

Article 42

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 38 (4),** the Commission shall submit to the Standing Committee on Medicinal Products for Human Use referred to in Article 214(1) a draft of the decision on the application, on the basis of the requirements set out in this Directive.

In duly justified cases, the Commission may return the opinion to the Agency **or 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 **38(5) or** 41(5), second subparagraph.

Where a draft decision differs from the opinion of the Agency **or of the coordination group**, the Commission shall provide a detailed explanation of the reasons for the differences.

The Commission shall send the draft decision to the competent authorities of the Member States and the 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 214(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 delivered by the Agency **or by the coordination group**, the Commission may refer the 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 applicant or 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 following 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 scope of the procedure initiated under Article 95 includes medicinal products covered by centralised marketing authorisation pursuant to Article 95(2), third 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 43

Granting of the national marketing authorisation

1. When a competent authority of the Member State grants a national marketing authorisation, it shall inform the applicant of the marketing authorisation of the summary of product characteristics, the package leaflet, the labelling as well as any conditions established in accordance with Articles 44 and 45 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 is in conformity with that accepted when the national marketing authorisation is granted or subsequently.

3. 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 labelling,** the package leaflet as well as any conditions established in accordance with Articles 44, 45 and any obligations imposed subsequently in accordance with Article 87, together with any deadlines for the fulfilment of those conditions and obligations for each medicinal product that they have authorised.

4. The competent authority of the Member State may consider and 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 summary of product characteristics shall be updated. **Such updates shall be made by the variation procedure or the application of the procedures laid down in Arftiele 40 or 41. For medicinal products authorised in accordance with Articles 34 or 36, the reference Member State and all concerned member States shall be involved. in accordance with tThe procedure referred to in Articles 38, 39 or 40 shall apply as appropriate.** if the additional evidence has an impact on the benefit-risk balance of a medicinal product. **If the summary of product characteristics has been updated in accordance with this paragraph, the Member State shall inform the reference Member State or the Member States concerned if the procedure referred to in Articles 34 and or 36 was applied.**

5. 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 environmental risk assessment and the pharmacovigilance system of the medicinal product concerned.

6. 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. The justification shall be provided separately for each therapeutic indication applied for.

Commented [A12]: SI: It should be considered whether it is necessary to prepare the PAR (public assessment report) also for generic and WEU (well established use) applications. The workload for NCAs should be considered.

7. The public assessment report referred to in paragraph **6**~~5~~ 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.

8. 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 as well as any conditions established in accordance with Articles 44, 45 and any obligations imposed subsequently in accordance with Article 87, together with any deadlines for the fulfilment of those conditions and obligations for each medicinal product that they have authorised.

Article 44

National marketing authorisation subject to conditions

1. A marketing authorisation for a medicinal product may be granted subject to one or more of the following conditions:
   (a) to take certain measures for ensuring 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 on the recording or reporting of suspected adverse reactions that are stricter than those referred to in Chapter IX;
   (d) any other conditions or restrictions with regard to the safe and effective use of the medicinal product;
   (e) the existence of an adequate pharmacovigilance system;
   (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 case of medicinal products for which there is ~~substantial~~ **specific** uncertainty as to the surrogate endpoint relation to the expected health outcome, where appropriate and relevant for the benefit-risk balance, a post-authorisation obligation to substantiate the clinical benefit;

(ga) in case of the environmental risk assessment suffering from deficiencies at the time of application, or if the risk identified in the environmental risk assessment has not been sufficiently addressed by the applicant, to address the deficiencies within an agreed timeframe and if required to implement appropriate risk mitigation measures;

(h) to conduct post-authorisation environmental risk assessment studies, collection of monitoring data or information on use, where identified or potential concerns about risks to the environment or public health, including antimicrobial resistance need to be further investigated after the medicinal product has been marketed;

(i) to conduct post-authorisation studies 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 88.

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

Article 45

National marketing authorisation under exceptional circumstances

1. In exceptional circumstances where, in an application under Article 6 for a marketing authorisation of a medical product, or in an application under Article 92 for a new therapeutic indication of an existing marketing authorisation, 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 derogation to Article 6, grant an authorisation under Article 43, subject to specific conditions, where the following requirements are met:

(a) the applicant has demonstrated, in the application file, that there are objective and verifiable reasons not to be able to submit comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use based on one of the grounds set out in Annex II;

(b) except for the data referred to in point (a), the application file 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 the validity of the national marketing authorisation shall be linked to the reassessment of the conditions set out in paragraph 1 after **~~the deadline specified by the competent authority or~~** two years **or within a shorter deadline specified by the competent authority** from the date when the new therapeutic indication was authorised or the marketing authorisation was granted, and thereafter at a risk-based frequency to be det~~va~~ermined by the competent authorities of the Member State and specified in the marketing authorisation.

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

Article 46

Validity and renewal of marketing authorisation

1. Without prejudice to paragraph 4, a 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 45(1) shall be valid for five years and be subject to renewal in accordance with paragraph 2.

By way of derogation from the first subparagraph, a 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 granted under paragraph 1, second or third subparagraph. Such application shall be submitted at least nine months before the national marketing authorisation ceases to be valid.

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.

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 marketing authorisation shall be valid for an unlimited period.

Article 47

Refusal of a national marketing authorisation

1. The national marketing authorisation shall be refused if, after verification of the particulars and documentations referred to in Article 6 and subject to the specific requirements laid down in Articles 9 to 14, the view is taken that:
   (a) the benefit-risk balance is not considered to be favourable;
   (b) that the applicant has not properly or sufficiently demonstrated the quality, safety or efficacy of the medicinal product;

(c) its qualitative and quantitative composition is not as declared;

(d) ~~the data for~~ the environmental risk assessment **is incomplete or insufficiently substantiated by the applicant or if the risks identified in the environmental risk assessment have not been sufficiently addressed by the applicant** ~~submitted by the applicant suffers from major deficiencies,~~ **unless post-authorisation environmental risk assessment studies can be requested or the identified risks can be mitigated with appropriate risk mitigation measures.** ~~it is considered, taking into account the benefit of the immediate availability of the medicinal product concerned~~ **, that those deficiencies shall be addressed with post-authorisation environmental risk assessment studies risks can be mitigated under a post authorisation obligation referred to in Article 44 (1) ga):** ~~is incomplete or insufficiently substantiated by the applicant or if the risks identified in the environmental risk assessment have not been sufficiently addressed by the applicant;~~

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

2. The national marketing authorisation shall also be refused if any particulars or documentations submitted in support of the application do not comply with Article 6, paragraphs 1 to 6, and Articles 9 to 14.

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

Section 7
Specific requirements for paediatric medicinal products

Article 48

Compliance with the paediatric investigation plan

1. The competent authority of the Member State for which an application for marketing authorisation or variation of a marketing authorisation is submitted under the provisions of this Chapter or of the Chapter VIII, shall verify whether it complies with the requirements laid down in Article 6(5).

2. Where the application is submitted in accordance with the procedure set out in this Chapter, Sections 3 and 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, as referred to in Article 148 of [revised Regulation (EC) No 726/2004] may, in the following cases, be requested to give its opinion as to whether studies conducted by the applicant are in compliance with the agreed paediatric investigation plan as defined in Article 74 of [revised Regulation (EC) No 726/2004]:
   (a) by the applicant, prior to submitting an application for a marketing authorisation or for a variation of a marketing authorisation;
   (b) by the competent authority of the Member State, when validating an application for a marketing authorisation or 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 an opinion drawn up 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 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 86.

Article 49

Data deriving from a paediatric investigation plan

1. Where a marketing authorisation or a variation of a marketing authorisation, is granted in accordance with the provisions under this Chapter or of the provisions under Chapter VIII:
   (a) the results of all clinical **and when appropriate non-clinical** studies, conducted in compliance with an agreed paediatric investigation plan as referred to in Article 6(5), point (a), shall be included in the summary of product characteristics and, if appropriate, in the package leaflet, or
   (b) any agreed waiver as referred to in Article 6(5), points (b) and (c), 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.

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 the provisions under this Chapter or of the provisions under Chapter VIII and which are protected either by a supplementary protection certificate under [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate, may be submitted under the procedure laid down in Articles 41 and 42.

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 I:

Subject matter, scope and definitions

Article 4
Definitions

(9) 'competent authorities' means the Agency and the competent authorities of the Members States;

(10) 'Agency' means the European Medicines Agency;

(11) 'non-clinical' means a study or a test conducted in vitro, 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 test may include simple and complex human cell-based assays, microphysiological systems including organ-on-chip, computer modelling, other non-human or human biology-based test methods, and animal-based tests;

(37) 'paediatric investigation plan' means a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population;

(38) 'paediatric population' means that part of the population aged between birth and 18 years;

(41) 'benefit-risk balance' means an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks referred to in point (35), subpoint (a);
