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**WORKING DOCUMENT**

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|---|---|
| From: | Presidency |
| To: | Delegations |
| No. prev. doc.: | 11863/24 |
| Subject: | Proposal for a Directive of the European Parliament and of the Council on the Union code relating to medicinal products for human use, and repealing Directive 2001/83/EC and Directive 2009/35/EC<br>Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006<br>- *Exchange of views* |

Delegations find in Annex the authorisations cluster to be discussed at the meetings of the Working Party on Pharmaceuticals and Medical Devices on 7-8 October 2024.

Changes compared to the Commission proposals are indicated in ~~strikethrough~~ for deletions and **bold/underline** for new text. In addition, changes compared to those made in document 11863/24 are highlighted in grey.

# Authorisations Cluster

# 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.

***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:**

**(…)**

**(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**

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 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**, 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')~~.

   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.

*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 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.

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 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 medicinal products 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 and the reference medicinal product, as set indicated in the application for the marketing authorisation**~~**.**

*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~~**t**he 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 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.

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 substance(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.

Recital

(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 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. **The active substance master file certificate does not conclusively assess the quality of an active ingredient and applicants may need to provide further quality evidence with regard to the final composition of the medicinal product and with regard to the safety, efficacy and indication of 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.

*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 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 [1].

# 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.

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

[1] 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.

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[2], 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.~~

[2] 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 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, ~~T~~**the 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 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, **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** 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**~~ **, 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[3], Council Directive 96/29/Euratom[4], Directive 2004/23/EC of the European Parliament and of the Council[5], Directive 2002/98/EC of the European Parliament and of the Council[6] and Directive 2010/53/EU of the European Parliament and of the Council[7].

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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3 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).

4 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).

5 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).

6 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).

7 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 can be requested**;

(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 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 year, on a renewable basis for the first three 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.

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;

   (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.

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

# REVISED DIRECTIVE

## 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 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;

(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 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;**