Council of the
European Union

Brussels, 28 April 2023
(OR. en)

8758/23

Interinstitutional File:
2023/0131(COD)

SAN 213
PHARM 59
MI 332
COMPET 362
VETER 45
ENV 418
RECH 146
CODEC 718
IA 82

COVER NOTE

From:	Secretary-General of the European Commission, signed by Ms Martine DEPREZ, Director
date of receipt:	26 April 2023
To:	Ms Thérèse BLANCHET, Secretary-General of the Council of the European Union
No. Cion doc.:	COM (2023) 193 final
Subject:	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

Delegations will find attached document COM(2023) 193 finalCOM (2023) 193 final.

Encl.: COM (2023) 193 final

EUROPEAN
COMMISSION

Brussels, 26.4.2023
COM(2023) 193 final

2023/0131 (COD)

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

(Text with EEA relevance)

{SEC(2023) 390 final} - {SWD(2023) 192 final} - {SWD(2023) 193 final} - {SWD(2023) 194 final}

EXPLANATORY MEMORANDUM

1. CONTEXT OF THE PROPOSAL

• Reasons for and objectives of the proposal

EU pharmaceutical legislation has enabled the authorisation of safe, efficacious and high-quality medicinal products. However, patient access to medicinal products across the EU and security of supply are growing concerns, mirrored by recent Council conclusions[1] and resolutions of the European Parliament[2]. There is also a growing problem of shortages of medicinal products for many EU/EEA countries. Consequences of such shortages include decreased quality of treatment received by patients and increased burden on health systems and on healthcare professionals, who need to identify and provide alternative treatments. While the pharmaceutical legislation creates regulatory incentives for innovation and regulatory tools to support timely authorisation of innovative and promising therapies, these products do not always reach the patient, and patients in the EU have differing levels of access.

Moreover, innovation is not always focused on unmet medical needs, and there are market failures, especially in the development of priority antimicrobials that can help address antimicrobial resistance. Scientific and technological developments and digitalisation are not fully exploited, while the environmental impact of medicinal products needs attention. In addition, the authorisation system could be simplified to keep up with global regulatory competition. The pharmaceutical strategy for Europe[3] is a holistic answer to the current challenges of the pharmaceutical policy with legislative and non-legislative actions interacting together to achieve its overall goal of ensuring EU's supply of safe and affordable medicinal products and supporting the EU pharmaceutical industry's innovation efforts[4]. Reviewing the pharmaceutical legislation is key to achieving these objectives. However, innovation, access and affordability are also influenced by factors outside the scope of this legislation, such as global research and innovation activities or national pricing and reimbursement decisions. Hence, not all problems can be addressed by the revision of the legislation alone. Despite this, EU pharmaceutical legislation can be an enabling and connecting factor for innovation, access, affordability and environmental protection.

The proposed revision of the EU pharmaceutical legislation builds on the high level of public health protection and harmonisation already achieved for the authorisation of medicinal products. The overarching aim of the reform is to ensure that patients across the EU have timely and equitable access to medicines. Another objective of the proposal is to enhance security of supply and address shortages through specific measures, including stronger obligations on marketing authorisation holders to notify potential or actual shortages and marketing withdrawals, cessations and suspensions in advance of a foreseen

---

1 Council conclusions on strengthening the balance in the pharmaceutical systems in the EU and its Member States (OJ C 269, 23.07.2016, p. 31). Council conclusions on access to medicines and medical devices for a stronger and resilient EU, 2021/C 269 I/02 (OJ C 269I, 7.7.2021, p. 3).

2 European Parliament resolution of 2 March 2017 on EU options for improving access to medicine (2016/2057(INI), European Parliament resolution of 17 September 2020 on the shortage of medicines – how to address an emerging problem (2020/2071(INI).

3 Communication from the Commission, *Pharmaceutical Strategy for Europe* (COM/2020/761 final), https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en.

4 Mission letter of the President of the European Commission to Stella Kyriakides, Commissioner for Health and Food Safety, mission-letter-stella-kyriakides_en.pdf (europa.eu)

interruption to continued supply of a medicinal product to the market. To support the sector's global competitiveness and innovative power, right balance needs to be struck between giving incentives for innovation, with more focus on unmet medical needs, and measures on access and affordability.

The framework needs to be simplified, adapted to scientific and technological changes, and contribute to reducing the environmental impact of medicinal products. This proposed reform is comprehensive but targeted and focuses on provisions relevant to achieving its specific objectives; therefore it covers all provisions apart from those concerning advertising, falsified medicinal products, and homeopathic and traditional herbal medicinal products.

Therefore, the objectives of the proposal are the following:

General objectives

– guarantee a high level of public health by ensuring the quality, safety and efficacy of medicinal products for EU patients;

– harmonise the internal market for the supervision and control of medicinal products and the rights and duties incumbent upon the competent authorities of the Member States.

Specific objectives

– make sure all patients across the EU have timely and equitable access to safe, effective, and affordable medicines;

– enhance security of supply and ensure medicines are always available to patients, regardless of where they live in the EU;

– offer an attractive innovation-and competitiveness friendly environment for research, development, and production of medicines in Europe;

– make medicines more environmentally sustainable.

All the general and specific objectives set out above are also relevant for the areas of medicinal products for rare diseases and for children.

- **Consistency with existing provisions in the policy area**

The current EU pharmaceutical legislation includes both general and specific legislation. Directive 2001/83/EC of the European Parliament and of the Council[5] and Regulation (EC) No 726/2004 of the European Parliament and of the Council[6] (together 'general pharmaceutical legislation') lay down provisions related to medicinal products authorisation and post-authorisation requirements, pre-authorisation support schemes, regulatory incentives in terms of data and market protection, manufacturing and supply, and the European Medicines Agency (EMA). The general pharmaceutical legislation is complemented by specific legislation on medicinal products for rare diseases (Regulation (EC) No 141/2000, the 'Orphan Regulation'[7]), medicinal products for children (Regulation

[5] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

[6] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

[7] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p. 1).

(EC) No 1901/2006, the 'Paediatric Regulation'[8]) and advanced therapy medicinal products (Regulation (EC) No 1394/2007, the 'ATMP Regulation'[9]). The proposed revision of the pharmaceutical legislation will consist of two legislative proposals:

– a new directive, repealing and replacing Directive 2001/83/EC and Directive 2009/35/EC of the European Parliament and of the Council[10] and incorporating relevant parts of the Paediatric Regulation (Regulation (EC) No 1901/2006)

– a new regulation, repealing and replacing Regulation (EC) No 726/2004, repealing and replacing the Orphan Regulation (Regulation (EC) No 141/2000) and repealing and incorporating relevant parts of the Paediatric Regulation (Regulation (EC) No 1901/2006).

The merger of the Orphan Regulation and the Paediatric Regulation with the legislation applicable to all medicinal products will allow for simplification and increased coherence.

Medicinal products for rare diseases and for children will continue to fall under the same provisions as any other medicinal product concerning their quality, safety and efficacy, for example concerning the marketing authorisation procedures, pharmacovigilance and quality requirements. However, specific requirements will also continue to apply to these types of medicinal products in order to support their development. This is because market forces alone have proven insufficient to stimulate adequate research and development of medicinal products for children and patients suffering from a rare disease. Such requirements, which are currently laid down in separate legislative acts, should be integrated into this regulation and the directive in order to ensure clarity and coherence of all the measures applicable to these products.

- **Consistency with other Union policies**

The EU pharmaceutical legislation described above has close links with several other related pieces of EU legislation. The 'Clinical Trials Regulation' (Regulation (EU) No 536/2014)[11]allows for more efficient approval of clinical trials in the EU. Regulation (EU) 2022/123[12] strengthens the role of the European Medicines Agency in order to facilitate a coordinated EU-level response to health crises. The EMA fees legislation[13] contributes to providing adequate financing for the EMA's activities, including respective remuneration to national competent authorities for their contribution to completing the EMA's tasks.

---

8 Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 378, 27.12.2006, p. 1).

9 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121).

10 Directive 2009/35/EC of the European Parliament and of the Council of 23 April 2009 on the colouring matters which may be added to medicinal products (OJ L 109, 30.4.2009, p. 10).

11 Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (OJ L 158, 27.5.2014, p. 1).

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

13 Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products, and Regulation (EU) No 658/2014 of the European Parliament and of the Council on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use (OJ L 35, 15.2.1995, p. 1).

There are also links with EU regulatory frameworks for other health products. EU legislation on blood, tissues and cells (BTC)[14] is relevant, as some substances of human origin are starting materials for medicinal products. The EU regulatory framework for medical devices[15] is also relevant, as there are products that combine medicinal products and medical devices.

Futhermore, the objectives of the proposed reform of the pharmaceutical legislation are consistent with those of a number of broader EU policy agendas and initiatives.

In terms of promoting innovation, Horizon Europe[16], a key funding programme for EU research and innovation, and Beating Cancer Plan[17] both support research and development of new medicinal products. In addition, innovation in the pharmaceutical sector is promoted by the intellectual property frameworks, on patents under the national patent laws, the European Patent Convention and the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement, and on supplementary protection certificates under the EU SPC Regulation[18]. The intellectual property action plan[19] under the Industrial Strategy includes modernising the system of supplementary protection certificates (SPCs). SPCs extend certain patent rights to protect innovation and compensate for lengthy clinical trials and marketing authorisation procedures. With regard to addressing unmet medical needs in the area of antimicrobial resistance, the proposed reform of the pharmaceutical legislation will contribute to the objectives of the European one health action plan against antimicrobial resistance (AMR)[20].

Concerning access to medicinal products, in addition to the pharmaceutical legislation, the intellectual property frameworks, the Health Technology Assessment (HTA) Regulation (Regulation (EU) 2021/2282)[21] and the Transparency Directive (Directive 89/105/EEC)[22] also play a role. In addition to extending certain patent rights to protect innovation, SPCs impact the effect of regulatory protection periods provided by the pharmaceutical

---

14 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, and 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 033, 8.2.2003, p. 30).

15 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p. 1) and Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (OJ L 117, 5.5.2017, p. 176).

16 Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe – the Framework Programme for Research and Innovation, laying down its rules for participation and dissemination, and repealing Regulations (EU) No 1290/2013 and (EU) No 1291/2013 (OJ L 170, 12.5.2021, p. 1).

17 Communication from the Commission, *Europe's Beating Cancer Plan* (COM/2021/44 final).

18 Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (OJ L 152, 16.6.2009, p. 1).

19 Communication from the Commission, *Making the most of the EU's innovative potential. An intellectual property action plan to support the EU's recovery and resilience* (COM/2020/760 final).

20 Communication from the Commission, *A European One Health Action Plan against Antimicrobial Resistance (AMR)*, https://ec.europa.eu/health/system/files/2020-01/amr_2017_action-plan_0.pdf.

21 Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (OJ L 458, 22.12.2021, p. 1).

22 Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems (OJ L 40, 11.2.1989, p. 8).

legislation and therefore the entry of generic and biosimilar medicinal products and ultimately patient access to medicinal products and affordability. Under the HTA Regulation, national HTA bodies will conduct joint clinical assessments that compare new medicinal products to existing ones. Such joint clinical assessments will help Member States take more timely and evidence-based decisions on pricing and reimbursement. Finally, the Transparency Directive regulates procedural aspects of the Member States' pricing and reimbursement decisions but does not effect the level of price.

In order to enhance security of supply of medicinal products, the proposed reform of the pharmaceutical legislation aims to address systemic shortages and supply chain challenges. The proposed reform therefore complements and further develops the roles of the Member States and competent authorities of the Member States as set out in the extension of the EMA mandate (Regulation (EU) 2022/123), and is aimed at ensuring access to and continued supply of critical medicinal products during health crises. It also complements the mission of the Health Emergency Preparedness and Response Authority (HERA) to ensure availability of medical countermeasures in preparation for and during health crises. The proposed reform of the pharmaceutical legislation is therefore consistent with the package of legislative initiatives related to health security under the European Health Union[23].

To address environmental challenges, the proposed reform of the pharmaceutical legislation will support initiatives under the European Green Deal[24]. These include the EU action plan 'Towards Zero Pollution for Air, Water and Soil' and the revision of: (i) the Urban Waste Water Treatment Directive[25], (ii) the Industrial Emissions Directive[26] and (iii) the list of surface and groundwater pollutants under the Water Framework Directive[27]. The proposal is also well aligned with the Strategic Approach to Pharmaceuticals in the Environment[28].

Finally, on the use of health data, the European Health Data Space[29] will provide a common framework across Member States for access to high-quality real world health data. This will promote progress in research and development of medicinal products and provide new tools for pharmacovigilance and comparative clinical assessments. By facilitating access to and use of health data, the two initiatives together will support the competitiveness and innovation capacity of the EU's pharmaceutical industry.

---

23 European Health Union - Protecting the health of Europeans and collectively responding to cross-border health crises, https://commission.europa.eu/strategy-and-policy/priorities-2019-2024/promoting-our-european-way-life/european-health-union_en.

24 Communication from the Commission. The European Green Deal. COM(2019) 640 final.

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

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

27 Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy (OJ L 327, 22.12.2000, p. 1) and Directive 2013/39/EU of the European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy Text with EEA relevance (OJ L 226, 24.8.2013, p. 1).

28 Strategic Approach to Pharmaceuticals in the Environment, https://ec.europa.eu/environment/water/water-dangersub/pharmaceuticals.htm.

29 Communication from the Commission, *A European Health Data Space: harnessing the power of health data for people, patients and innovation* (COM(2022) 196 final).

2. LEGAL BASIS, SUBSIDIARITY AND PROPORTIONALITY

- **Legal basis**

The proposal is based on Articles 114(1) and 168(4), point (c), of the Treaty on the Functioning of the European Union (TFEU). This is consistent with the legal basis of existing EU pharmaceutical legislation. Article 114(1) has as its object the establishment and functioning of the internal market, while Article 168(4), point (c), relates to the setting of high standards for the quality and safety of medicinal products.

- **Subsidiarity (for non-exclusive competence)**

Common standards of quality, safety and efficacy for the authorisation of medicinal products constitute a cross-border public health issue that affects all Member States and thus can be regulated effectively only at EU level. EU action relies also on the single market to achieve a stronger impact as regards access to safe, effective and affordable medicinal products, and with regard to the security of supply across the EU. Uncoordinated measures by Member States may result in distortions of competition and barriers to intra-EU trade for medicinal products that are relevant for the entire EU, and would also likely increase administrative burden for pharmaceutical companies, which often operate in more than one Member State.

A harmonised approach at EU level also provides greater potential for incentives to support innovation and for concerted action to develop medicinal products in areas of unmet medical needs. Moreover, simplification and streamlining of processes under the proposed reform are expected to reduce administrative burden for companies and authorities and hence improve the efficiency and attractiveness of the EU system. The reform will also have a positive influence on the competitive functioning of the market through targeted incentives and other measures that facilitate early market entry of generic and biosimilar medicinal products, contributing to patient access and affordability. Nevertheless, the proposed reform of the pharmaceutical legislation respects Member States' exclusive competence in the provision of health services, including pricing and reimbursement policies and decisions.

- **Proportionality**

The initiative does not go beyond what is necessary to achieve the objectives of the reform. It does so in a way that is conducive to national action, which would otherwise not be sufficient to achieve those objectives in a satisfactory way.

The principle of proportionality has been reflected in the comparison of different options evaluated in the impact assessment. For example, trade-offs are inherent between the objective of innovation (promoting the development of new medicinal products) and the objective of affordability (which is often achieved by generic/biosimilar competition). The reform maintains the incentives as a key element for innovation, but they are adapted to better encourage and reward product development in areas of unmet medical needs and to better address timely patient access to medicinal products in all Member States.

- **Choice of the instrument**

The proposed regulation introduces a large number of amendments to Regulation (EC) No 726/2004. It also incorporates part of the current provisions and amendments to Regulation (EC) No 1901/2006, as well as current provisions and amendments to Regulation (EC) No 141/2000. A new regulation repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006 (rather than an amending regulation) is therefore considered the appropriate legal instrument.

3. RESULTS OF EX-POST EVALUATIONS, STAKEHOLDER CONSULTATIONS AND IMPACT ASSESSMENTS

- **Ex-post evaluations/fitness checks of existing legislation**

For the reform of the general pharmaceutical legislation, stakeholder consultation activities were carried out as part of the 'back-to-back' evaluations and impact assessments of the general pharmaceutical legislation and of the Orphan and Paediatric Regulations[30].

For medicinal products for rare diseases and for children a joint evaluation on the functioning of the two pieces of legislation was carried out and published in 2020[31].

For the general pharmaceutical legislation the evaluation of the legislation showed that the legislation continues to be relevant for the dual overarching objectives of protecting public health and harmonising the internal market for medicinal products in the EU. The legislation delivered on the objectives of the 2004 revision, albeit not to the same extent for all. The objective of ensuring quality, safety and efficacy of medicinal products was achieved to the largest extent, while patient access to medicinal products in all Member States was achieved only to a limited extent. As to ensuring the competitive functioning of the internal market and attractiveness in a global context, the legislation has performed to a moderate extent. The evaluation found that the achievements or shortcomings of the 2004 revision vis-a-vis its objectives depend on many external factors outside the remit of the legislation. These include R&D activities and international location of R&D clusters, national pricing and reimbursement decisions, business decisions and market size. The pharmaceutical sector and the development of medicinal products are global; research and clinical trials conducted on one continent will support development and authorisation in other continents; global are also the supply chains and manufacturing of medicinal products. International cooperation to harmonise requirements to support authorisation exists, e.g. the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use[32].

The evaluation identified the main shortcomings that the pharmaceutical legislation has not adequately addressed, while recognising that these also depend on factors outside its remit. These main shortcomings are as follows:

– Medical needs of patients are not sufficiently met.

– Affordability of medicinal products is a challenge for health systems.

– Patients have unequal access to medicinal products across the EU.

– Shortages of medicinal products are an increasing problem in the EU.

– The medicinal product life cycle can have negative impacts on the environment.

– The regulatory system does not sufficiently cater for innovation and in some instances creates unnecessary administrative burden.

Concerning medicinal products for rare diseases and for children, the evaluation showed that overall the two specific pieces of legislation have achieved positive results by allowing more medicinal products to be developed for these two population groups. However, it also

---

30 Commission staff working document, Impact Assessment, Annex 5: Evaluation.

31 Evaluation of the medicines for rare diseases and children legislation, https://health.ec.europa.eu/medicinal-products/medicines-children/evaluation-medicines-rare-diseases-and-children-legislation_en.

32 ICH – harmonisation for better health, https://www.ich.org/.

identified important shortcomings, which are similar to the ones identified for the general pharmaceutical legislation:

– Medical needs of patients with rare diseases and of children are not sufficiently met.

– Affordability of medicinal products is a growing challenge for health systems.

– Patients have unequal access to medicinal products across the EU.

– The regulatory system does not sufficiently cater for innovation and in some instances creates unnecessary administrative burden.

- **Stakeholder consultations**

For the reform of the general pharmaceutical legislation, stakeholder consultation activities were carried out as part of the 'back-to-back' evaluation and impact assessment[33]. A single consultation strategy was prepared for this exercise, including consultation activities looking backward and forward. It aimed to collect inputs and perspectives of all stakeholder groups both on the evaluation of the legislation and for the impact assessment of different possible policy options for the reform.

The following key stakeholder groups were identified as priority groups in the consultation strategy: the public; organisations representing patients, consumers and civil society active in public health and social issues ('CSOs'); healthcare professionals and healthcare providers; researchers, academia and learned societies (academics); environmental organisations; the pharmaceutical industry and their representatives.

As part of the internal policy work process supporting the revision, the Commission collaborated with the European Medicines Agency (EMA) and the competent authorities of the Member States (NCAs) dealing with the regulation of medicinal products. Both actors play a pivotal role in implementing the pharmaceutical legislation.

Information was collected through consultations that took place between 30 March 2021 and 25 April 2022. These consisted of:

– feedback on the Commission's combined evaluation roadmap/inception impact assessment (30 March-27 April 2021);

– Commission online public consultation (28 September-21 December 2021);

– targeted stakeholder surveys with public authorities, the pharmaceutical industry including SMEs, academia, civil society representatives and healthcare providers (survey) (16 November 2021-14 January 2022);

– interviews (2 December 2021-31 January 2022);

– a validation workshop on the evaluation findings (workshop-1) on 19 January 2022;

– a validation workshop on the impact assessment findings (workshop 2) on 25 April 2022.

There was broad consensus among stakeholders that the current pharmaceutical system guarantees a high level of patient safety on which the revision can build to address new challenges and improve supply of safe and affordable medicinal products, patient access and innovation, especially in areas where the medical needs of patients are not met. The public, patients and civil society organisations expressed their expectation of equitable

[33] Commission staff working document, Impact Assessment, Annex 2: Stakeholder Consultation (Synopsis Report).

access to innovative therapies across the EU, including for unmet medical needs, and continuous supply of their medicinal products. Public authorities and patient organisations opted for a variable duration for the current main incentives, as reflected in the preferred option. The pharmaceutical industry argued against any introduction of variable incentives or the shortening of existing ones and favoured the introduction of additional or novel incentives. Industry also highlighted the need for stability in the current legal framework and predictability for incentives. The elements on the environment, regulatory support for non-commercial entities and repurposing of medicinal products included in the preferred option were supported by key stakeholders such as healthcare providers, academia and environmental organisations.

Concerning the revision of the legislation on medicinal products for children and for rare diseases, specific consultation activities were carried out in the context of the impact assessment procedure: a public consultation ran from 7 May to 30 July 2021. Furthermore, targeted surveys, including a costing survey both for pharmaceutical companies and public authorities, were conducted from 21 June to 30 July 2021 (late responses were accepted until the end of September 2021, due to the summer break). An interview programme with all relevant stakeholder groups (public authorities, pharmaceutical industry including SMEs, academia, civil society representatives and healthcare providers) was conducted at the end of June 2021, while focus groups met on 23 February 2022 to discuss some of the main issue of the revision.

There was broad consensus among stakeholders that the two pieces of legislation have had a positive effect on the development of medicinal products for children and the treatment of rare diseases. However, concerning the Paediatric Regulation, all the current structure of the paediatric investigation plan and of the condition allowing the waiver of the obligation to draw up such a plan were considered as possible obstacles to the development of certain innovative products. All stakeholders highlighted that for both the medicinal products for rare diseases and the medicinal products for children, medicinal products addressing unmet medical needs of patients should be better supported. Public authorities supported a variable duration for market exclusivity for medicinal products for rare diseases as a tool to better focus development in areas where treatments are not available. The pharmaceutical industry argued any introduction of variable incentives or the shortening of existing ones and favoured the introduction of additional or novel incentives. As for the revision of the general pharmaceutical legislation, industry also highlighted the need for stability in the current legal framework and predictability for incentives.

- **Collection and use of expertise**

In addition to the extensive stakeholder consultation described in previous sections, the following external studies were conducted to support the 'back-to-back' evaluation and impact assessment of the general pharmaceutical legislation and the evaluation and impact assessment of the orphan and paediatric legislation:

– *Study supporting the Evaluation and Impact Assessment of the general pharmaceutical legislation. Evaluation Report*, Technopolis Group (2022).

– *Study supporting the Evaluation and Impact Assessment of the general pharmaceutical legislation. Impact Assessment Report*, Technopolis Group (2022).

– *Future-proofing pharmaceutical legislation - Study on medicine shortages*, Technopolis Group (2021).

– *Study to support the evaluation of the EU Orphan Regulation*, Technopolis Group and Ecorys (2019).

– *Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe*, Copenhagen Economics (2018).

– *Study on the economic impact of the Paediatric Regulation, including its rewards and incentives*, Technopolis Group and Ecorys (2016).

- **Impact assessments**

General pharmaceutical legislation

The impact assessment for the revision of the general pharmaceutical legislation[34] analysed three policy options (A, B and C).

– Option A builds on the status quo and achieves the objectives mainly through new incentives.

– Option B reaches the objectives through more obligations and oversight.

– Option C adopts a 'quid pro quo' approach in the sense that positive behaviour is rewarded and obligations are only used when there are no alternatives.

Option A maintains the current system of regulatory protection for innovative medicinal products and adds additional conditional periods of protection. Priority antimicrobials benefit from a transferable exclusivity voucher. Current requirements on security of supply are retained (notification of withdrawal at least 2 months in advance). The existing requirements on the environmental risk assessment continue with additional information obligations.

Option B provides for a variable duration of regulatory data protection periods (split into standard and conditional periods). Companies must either have an antimicrobial in their portfolio or pay into a fund to finance the development of new ones. Companies are obliged to launch medicinal products with an EU-wide authorisation in the majority of Member States (small markets included) and to provide information on public funding received. Current requirements on security of supply are retained and companies are obliged to offer their marketing authorisation for transfer to another company before withdrawal. The environmental risk assessment results in additional responsibilities for companies.

Option C provides for a variable duration of regulatory data protection (split into standard and conditional periods), striking a balance between providing attractive incentives for innovation and supporting timely patient access to medicinal products across the EU. Priority antimicrobials can benefit from a transferable exclusivity voucher subject to strict eligibility criteria and conditions for use of the voucher, while prudent-use measures further contribute to addressing antimicrobial resistance. Marketing authorisation holders are required to ensure transparency on public funding for clinical trials. Reporting of shortages is harmonised and only critical shortages are brought to the attention of authorities at the EU level. Marketing authorisation holders are obliged to notify possible shortages earlier and to offer their marketing authorisation for transfer to another company before withdrawal. Requirements on the environmental risk assessment and conditions of use are strengthened.

All options are complemented by a set of common elements aimed at simplifying and streamlining regulatory procedures and future-proofing the legislation with a view to accommodating novel technologies.

[34] Commission staff working document, Impact Assessment.

The preferred option is based on option C and also includes the common elements mentioned above. The preferred option was considered to be the best policy choice, taking into account the specific objectives of the reform and the economic, social and environmental impacts of the proposed measures.

The preferred option and its introduction of variable incentives is a cost-effective way of achieving the objectives of improved access, addressing unmet medical need and affordability for health systems. It is expected to provide 8% increased access, meaning 36 million more people residing in the EU who can potentially benefit from a new medicinal product, EUR 337 million in annual gains for public payers, and more medicinal products addressing unmet medical needs. In addition, savings are expected for companies and regulatory authorities through the cross-cutting measures that would allow for better coordination, simplification and accelerated regulatory processes.

Measures to incentivise the development of priority antimicrobials are estimated to entail costs for public payers and the generic industry but could be effective against antimicrobial resistance if applied under strict conditions and with tight measures for prudent use. These costs must also be seen in the context of the threat of resistant bacteria and current costs incurred from antimicrobial resistance including deaths, healthcare costs and productivity losses. The principal costs for industry are associated with shorter default regulatory data protection period and conditions for extensions of regulatory data protection, and with increased reporting on shortages and environmental risks. Regulatory authorities will incur costs to perform additional tasks in the areas of shortage management, strengthened environmental risk assessment and enhanced pre-authorisation scientific and regulatory support.

Orphan and paediatric legislation

The impact assessment on the revising of the *orphan* and *paediatric* legislation also analysed three policy options (A, B and C) per legislative act. The different policy options vary as to the incentives or rewards to which medicinal products for rare diseases and for children would be entitled. In addition, the revision will include a series of common elements present in all options.

For medicinal products for *rare diseases*, option A keeps the 10 years of market exclusivity and adds - as an additional incentive - a transferable regulatory protection voucher for products addressing a high unmet medical need (HUMN) of patients. Such a voucher allows for a one-year extension in the length of regulatory protection or can be sold to another company and used for a product in that company's portfolio.

Option B abolishes the current market exclusivity of 10 years for all orphan medicinal products.

Option C provides for a variable duration of market exclusivity of 10, 9 and 5 years, based on the type of orphan medicinal product (for HUMN, new active substances and well-established use applications respectively). A 'bonus' market exclusivity extension of 1 year can be granted, based on patient accessibility in all relevant Member States, but only for HUMN products and new active substances.

All options are complemented by a set of common elements aimed at simplifying and streamlining regulatory procedures and future-proofing the legislation.

Option C was considered to be the best policy choice, taking into account the specific objectives and the economic and social impacts of the proposed measures. This option is expected to provide a balanced positive outcome contributing to the achievement of the four objectives of the revision. It will aim to refocus investments and boost innovation, in

particular in products addressing HUMN, without undermining the development of other medicinal products for rare diseases. The measures provided for under this option are also expected to improve the competitiveness of EU pharmaceutical industry, including of SMEs, and will lead to the best results in terms of patient access (due to: (i) the possibility for generics and biosimilars to enter the market earlier than they do today; and (ii) the proposed access conditionality for extending the market exclusivity). Furthermore, more flexible criteria to better define an orphan condition will make the legislation more 'fit' to accommodate new technologies and reduce administrative burdens.

The total balance of yearly costs and benefit calculated per interested stakeholder group for this preferred option compared to the baseline are: EUR 662 million cost savings for public payers from accelerated generic entry and a EUR 88 million profit gain for the generic industry. The public will benefit from additional 1 or 2 HUMN medicinal products and overall broader and faster access for patients. Originators will see an estimated EUR 640 million gross profit loss from earlier generic entry, but savings are expected for companies through the cross-cutting measures in the general pharmaceutical legislation that would allow for better coordination, simplification and accelerated regulatory processes.

For medicinal products *for children*, in option A the 6-month supplementary protection certificate (SPC) extension is kept as a reward for all medicinal products completing a paediatric investigation plan ('PIP'). Furthermore, an extra reward benefiting products addressing unmet medical needs of children is added. This will consist of either 12 extra months of SPC extension or a regulatory protection voucher (duration 1 year), which could be transferred to another product (possibly of another company) against payment, allowing the receiving product to benefit from extended regulatory data protection (+1 year). In option B, the reward for completing a PIP is abolished. Developers of every new medicinal product would continue to be obliged to agree with the EMA and conduct a PIP, but the extra costs incurred would not be rewarded. In option C, like today, the 6-month SPC extension remains the main reward for completing a PIP. All options are complemented by a set of common elements aimed at simplifying and streamlining regulatory procedures and future-proofing the legislation.

Option C was considered the best policy choice, taking into account the proposed measures' specific objectives and economics and social impacts. Option C is expected to yield to an increased number of medicinal products, in particular in areas of unmet medical needs of children, which are expected to reach children faster than today. It would also ensure a fair return of investment for medicinal products developers who fulfil the legal obligation to study medicinal products in children, as well as reduced administrative costs linked to the procedures that follow from the obligation.

New simplification measures and obligations (for example those linked to medicinal product's mechanism of action) are expected to cut time to access to children's versions of medicinal products by 2-3 years and to bring three more new medicinal products for children yearly compared to the baseline, which in turn results in additional rewards for developers. These new medicinal products for children will result, on a yearly basis, in costs for the public estimated EUR 151 million, while originator companies would gain EUR 103 million in gross profits to compensate their efforts. Thanks to simplification of the rewards scheme linked to the study of medicinal products for use in children, generic companies will find it easier to predict when they will be able to enter the market.

- **Regulatory fitness and simplification**

The proposed revisions aim to simplify the regulatory framework and improve its effectiveness and efficiency, thereby reducing the administrative costs borne by companies

and competent authorities. Most of the envisaged measures will act on core procedures for the authorisation and life cycle management of medicinal products.

Administrative costs will fall for competent authorities, business and other relevant entities, for two overarching reasons. Firstly, procedures will be streamlined and accelerated, for example in connection with the renewal of marketing authorisations and the submission of variations or the transfer of the responsibility for orphan designations from the Commission to the EMA. Secondly, there will be enhanced coordination of the European medicines regulatory network, for example in terms of the work of different EMA committees and interactions with related regulatory frameworks. Further contributions to cost reductions for business and administrations are expected to come from adaptations to accommodate new concepts such as adaptive clinical trials, a medicinal product's mechanism of action, use of real world evidence, and new uses of health data within the regulatory framework.

Enhanced digitisation will facilitate the integration of regulatory systems and platforms across the EU and support for the re-use of data, and is expected to reduce costs for administrations over time (although it may induce initial one-off costs). For example, electronic submissions by industry to the European Medicines Agency and competent authorities of the Member States will deliver cost savings to industry. Moreover, the envisaged use of the electronic product information (as opposed to paper leaflets) should also lead to administrative cost reductions.

SMEs and non-commercial entities involved in the development of medicinal products are expected to benefit in particular from the envisaged simplification of procedures, wider use of electronic processes and reduction of administrative burden. The proposal also aims at optimising the regulatory support (e.g. scientific advice) to SMEs and non-commercial organisations, resulting in additional reductions of administrative costs for these parties.

Overall, the envisaged measures for simplification and burden reduction are expected to reduce costs for businesses, supporting the 'one in one out' approach. In particular, the proposed streamlining procedures and enhanced support are expected to yield cost savings for EU pharmaceuticalindustry.

- **Fundamental rights**

The proposal contributes to achieving a high level of human health protection and is therefore consistent with Article 35 of the Charter of Fundamental Rights of the European Union.

4. BUDGETARY IMPLICATIONS

The budgetary implications are set out in the legislative financial statement attached to the proposal.

Budgetary implications are mainly related to additional tasks to be carried out by the European Medicines Agency in terms of providing scientific, administrative and IT support in the following main areas:

– enhanced pre-authorisation scientific and regulatory support;

– decision-making on orphan designations and management of the Union Register of designated orphan medicinal products;

– active substance master file assessment and certification;

– inspection capacities for inspections in third countries and support to Member States;

– environmental risk assessment strengthening;

– shortage management and security of supply.

5. OTHER ELEMENTS

- **Implementation plans and monitoring, evaluation and reporting arrangements**

The development of new medicinal products can be a long process that can take up to 10-15 years. Incentives and rewards therefore have an influence many years after the marketing authorisation date. The benefit for patients also needs to be measured over a period of at least 5-10 years after a medicinal product is authorised. The Commission intends to monitor relevant parameters that enable assessment of progress of the proposed measures with a view to reaching their objectives. The majority of indicators are already collected at the EMA level. Furthermore, the Pharmaceutical Committee[35] will provide a forum for discussing issues related to the transposition and monitoring progress. The Commission will report on the monitoring periodically. A meaningful evaluation of the results of the revised legislation can only be envisaged after at least 15 years from its entry into application.

- **Detailed explanation of the specific provisions of the proposal**

The proposed revision of the pharmaceuticals legislation consists of a proposal for a new regulation and a proposal for a new directive (see previous section 'Consistency with existing provisions in the policy area'), which will also cover orphan and paediatric medicinal products. Provisions for orphan medicinal products have been integrated in the proposed regulation. For paediatric medicinal products, procedural requirements applicable to these products are primarily integrated in the proposed regulation, while the general framework for the authorisation and rewarding of these products has been included in the new directive. The main areas of revision under the proposed new directive are covered by the explanatory memorandum for the accompanying proposal for a directive.

The proposed regulation includes the following main areas of revision:

Promoting innovation and access to affordable medicines creating a balanced pharmaceutical ecosystem

To enable innovation and promote the competitiveness of the EU pharmaceutical industry, in particular small and medium-sized firms, the provisions of the proposed regulation work in synergy with those of the proposed directive.

In this respect, a balanced system of incentives is proposed. The system rewards innovation, especially in areas of unmet medical need, and innovation reaches patients and improves access across the EU, including for medicines for rare diseases. To make the regulatory system more efficient and innovation-friendly, measures are proposed to simplify and streamline procedures and to create an agile and future-proof framework (see the measures proposed further below under '*Reducing regulatory burden and providing a flexible regulatory framework to support innovation and competitiveness'* and in the proposed directive).

Modulation of the length of the market exclusivity for orphan medicinal products

The proposed regulation continues to provide measures to promote research, development and authorisation for medicinal products to address the unmet medical needs of people

[35] Council Decision of 20 May 1975 setting up a pharmaceutical committee (75/320/EEC).

living with rare diseases, and it targets more those areas of high unmet medical needs (HUMN), where research is most needed and investment is riskier. Criteria to identify medicinal products addressing HUMN are set out in the regulation. The duration of market exclusivity is set at [nine] years, except for: (i) orphan medicinal products addressing HUMN, which will get [ten] years, and (ii) well-established use orphan medicinal products, which will be granted [five] years of market exclusivity. A 'bonus' market exclusivity extension of [one] year can be granted, based on patient access in all relevant Member States.

To continue supporting further development of an already authorised orphan medicinal product, while avoiding ever-greening, the first two new indications of an orphan medicinal product will be rewarded with [one] year of exclusivity each. The extension will apply to the entire medicinal product.

Therefore, the modulation of market exclusivity, while keeping the orphan medicinal products reward system very competitive compared to other regions, will better reward medicinal products that will address diseases for which no treatment is available or medicinal products that will bring exceptional advances in treatment. Furthermore, the new system will also promote faster generic/biosimilar competition improving affordability and patient access to orphan medicinal products.

Paediatric investigation plans for medicinal products for children, based on a medicinal product's mechanism of action

Currently, the obligation to conduct a paediatric investigation plan (PIP) for studies in children is waived in certain situations, for example when an adult product is intended for a disease not existing in children. However, in certain cases the molecule in question, due to its molecular mechanism of action, may be efficacious against a disease in children that is different from the one for which it was initially designed for use in adults.

The proposal envisages that in such cases, the product will have to be studied for use in children too. This requirement, apart from increasing the number of medicinal products adequately studied for use in children, is also expected to promote innovation and research.

Measures related to antimicrobials

To promote the development of priority antimicrobials that can address antimicrobial resistance, transferable data exclusivity vouchers are introduced. To this end, strict criteria are laid down for defining the categories of priority antimicrobials eligible to receive the voucher.

Such a voucher will grant an additional year of regulatory data protection to the developer of the priority antimicrobial, which the developer can either use for any product in their own product portfolio or sell it to another marketing authorisation holder.

The number of vouchers will be limited to a maximum of 10 over a 15 year period. Transparency regarding any contribution to the research & development costs for priority antimicrobials will be ensured. Strict conditions are also introduced for the transfer and use of the voucher to extend the data protection period of another product within a certain period, to ensure predictability for competitor products, including generics and biosimilars.

Eligibility criteria and the validity of the voucher are also linked to obligations to supply the priority antimicrobial in the EU. A sunset period of 15 years is proposed, after which time the Parliament and the Council may decide to continue or review the measure, following a proposal by the Commission, based on experience gained during this period.

Antimicrobial prudent use measures require that antimicrobials are placed under prescription status in the EU. Antimicrobial marketing authorisation holders are required to develop a stewardship plan for antimicrobial resistance which includes information on risk mitigation measures, monitoring and reporting of resistance to the medicinal product.

The environmental fate of the antimicrobial, including through its manufacture and disposal, becomes a factor to be assessed in the environmental risk assessment. The proposal reinforces its provisions on package sizes, educational measures and proper disposal of unused and expired antimicrobials.

Enhanced pre-authorisation scientific and regulatory support

Scientific and regulatory support by the European Medicines Agency will be strengthened, in particular for developers of medicinal products that address unmet medical needs, e.g. by building on the experience gained with the PRIME scheme and procedures used during the COVID-19 pandemic, such as a phased review of data. It will provide an enhanced legal framework for such scientific support and accelerated assessment and authorisation of medicinal products that offer an exceptional therapeutic advancement in areas of unmet medical needs including orphan medicinal products in particular for HUMN.

Small and medium-sized firms and not-for-profit entities will benefit from a dedicated support scheme composed of regulatory, procedural and administrative support, which will also include a reduction, deferral or waiver of fees. In addition, the regulation facilitates the translation of robust research results, carried out by not-for-profit entities, onto the label, allowing new promising therapeutic indications of off-patent medicinal products for unmet medical needs.

Moreover, the European Medicines Agency will be able to provide scientific advice to developers in parallel with the scientific advice given by HTA bodies under the 'HTA Regulation' or by expert panels under the 'Medical Device Regulation'. The European Medicines Agency will also be able to consult other relevant Member State authorities (e.g. with clinical trial expertise) in its scientific advice activities.

These measures are designed to help medicine developers generate clinical evidence that meets the needs of the different authorities along the medicinal products' life cycle, while respecting the different remits of the legal frameworks concerned.

In addition, the European Medicines Agency will be able to provide scientific opinions related to the classification of products, thereby advising developers and regulators on whether a particular product under development is a medicinal product or not.

Finally, the European Medicines Agency will coordinate a mechanism for consulting public authorities active along the medicinal product life cycle, to promote the sharing of information and the pooling of knowledge on general issues of scientific or technical nature that are relevant for developing, evaluating and accessing medicinal products.

Temporary emergency marketing authorisation

In a public health emergency, it is of major interest for the EU that safe and efficacious medicinal products can be developed and made available within the EU as soon as possible. Agile, fast and simplified processes are of the essence. A range of measures already exist at EU level to facilitate, support and speed up the development of and marketing authorisation for treatments and vaccines during a public health emergency.

The proposed regulation introduces the possibility to grant temporary emergency marketing authorisations to address public health emergencies. Such authorisations should be granted provided that the benefit of the immediate availability of the medicinal product

in question on the market, with regard to the circumstances of the public health emergency, outweighs the risk inherent in the fact that additional comprehensive quality, non-clinical, clinical data may not yet be available (though they should still be required at a later stage).

Improving security of supply of medicines

Addressing shortages of medicines

The proposal sets out a framework for the activities to be deployed by the Member States and the Agency to improve the EU's capacity to react efficiently and in a coordinated manner to support shortage management and security of supply of medicinal products, in particular critical medicinal products, to EU citizens, at all times. The provisions to strengthen the security of supply of medicines in the EU were, in part, informed by a structured dialogue with and between the actors in the pharmaceuticals manufacturing value chain and public authorities.

This proposal complements and further develops the core tasks already given to the Agency in the extension of its mandate (Regulation (EU) 2022/123) which was introduced as part of the EU's overall health response to the COVID-19 pandemic and the improved crisis management framework. It also complements Health Emergency Preparedness and Response Authority's (HERA) mission to ensure availability of medical countermeasures in preparation for and during crises.

EMA capacity to inspect sites located in non-EU countries

Challenges in inspection capacity and capability in the EU network have been evident and these gaps have been further exacerbated because of the COVID-19 pandemic. In some cases, the lack of resources has led to delayed inspections of EU interest. Solutions are needed to promote and support extra inspection capacity and build inspector capability, to strengthen the oversight of compliance with good practice by sites located outside the EU. Changes to the legal framework will allow the European Medicines Agency to have the necessary authority and expertise to conduct certain inspections of EU interest also in emergency situations, and when specific capacity and expertise is required.

Joint Audit Programme

To maintain an equivalent and harmonized implementation of the EU legislation on good manufacturing, clinical and distribution practices, and the corresponding enforcement activities, the new legal framework establishes, within the EMA, the Joint Audit Programme (JAP) to ensure that the Member States' inspectorates are subject to regular audits conducted by other Member States.

Furthermore, the JAP will be an essential tool for mutual recognition agreements and other international agreements, as it gives evidence of a regulatory system for medicinal products based on a network of EU agencies that operate to consistent best practice standards.

Reducing regulatory burden and providing a flexible regulatory framework to support innovation and competitiveness

Improved structure and governance of EMA and the regulatory network

The agility of the European regulatory system is a key component for attracting applicants and developers of medicinal products, from generics and biosimilars to cutting edge medicines. The evaluation and assessment of medicinal products in the EU relies on the EMA, competent authorities of the Member States and their experts who are present in the scientific committees of the EMA.

Both EMA scientific committees and competent authorities of the Member States are faced with an increasing number of procedures, which require additional resources to ensure that rapporteurs and assessors continue to be available to conduct assessment within the appropriate timeframe. Moreover, new challenges arise from the assessment of innovative and complex medicinal products. Capacity limitations that were observed during the COVID-19 pandemic risk becoming more frequent.

It is therefore essential to continue to optimise the functioning and efficiency of the regulatory system. In this regard, duplication of work needs to be avoided and procedures should be handled in the most efficient way.

However, the current structure of the EMA means that in some cases up to five scientific committees are involved in assessing a single medicinal product. Therefore, the structure of the EMA scientific committees is simplified and reduced to two main Committees: the Committee for Medicinal Products for Human Use (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC) as the main safety committee.

The expertise of the Committee for Advanced Therapies (CAT), the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO) and the Committee for Herbal Medicinal Products (HMPC) will be retained and reorganised in the form of working parties and a pool of experts who will give input to the CHMP, PRAC and the Co-ordination Group for Mutual Recognition and Decentralised Procedures -Human (CMDh).

The CHMP and PRAC will consist, like today, of experts from all Member States, and especially in the CHMP, the voice of patients will be strengthened by appointing patient representatives to this committee for the first time.

Working parties will support the work of the committees and will mostly consist of experts appointed by the Member States based on their expertise and of external experts. This will ensure a continuous link between the experts in the competent authorities of the Member States and the EMA. The model of rapporteurs remains unchanged.

Representation of patients and health care professionals with expertise in all areas, including rare and paediatric diseases, will be increased at the CHMP and PRAC, in addition to the dedicated working parties that represent patients and health care professionals.

This simplified structure is expected to free up resources for the network to focus on new activities, in particular regarding early scientific support for promising medicinal products and repurposing, as well as activities related to more of a life cycle approach to authorising medicinal products.

Training opportunities will be provided so that all Member States build expertise in new areas of science and technology, so they can actively contribute to the work of the regulatory network in assessing and monitoring medicinal products, including cutting edge innovative and complex medicinal products.

Responsibility for adopting decisions on orphan designations will be transferred from the Commission to the Agency to provide a more effective and efficient procedure.

Other simplification, streamlining and future proofing measures

Reduction of the regulatory burden will be facilitated by measures to simplify regulatory procedures and increased digitalisation, including provisions related to the electronic submission of applications for marketing authorisation and electronic product information (ePI) on authorised medicinal products.

Among the measures to reduce the regulatory burden are the abolishment of the renewal and the sunset clause. The simplification of the structure of the scientific committees at the EMA should also reduce the regulatory burden for companies and simplify their interactions with the EMA.

The reduction of administrative burden through simplification and digitalisation measures will benefit in particular small and medium-sized firms and not-for-profit entities involved in the development of medicinal products. Moreover, a number of measures will contribute to ensuring that the regulatory framework will be able to deal with emerging developments in science. This includes provisions related to adapted clinical trials, use of real-world evidence, secondary use of health data and regulatory sandboxes.

A regulatory sandbox can under certain conditions be linked to an adapted framework, tailored to the characteristics or methods inherent to certain, especially novel medicines, without lowering the high standards of quality, safety and efficacy. Measures for adapted frameworks are provided for in the proposed Directive.

Taken together, the various measures in the proposed regulation and directive addressing simplification to support innovation, future proofing and reduction of the regulatory burden will strengthen the competitiveness of the pharmaceutical sector.

Evolutionary and simplified Paediatric Investigation Plans (PIPs)

For certain type of paediatric developments, the necessity to submit and agree with the EMA, at a very early stage, a full clinical development plan for studies in children, is problematic. In certain cases, this obliges developers to make assumptions about the expected results.

This results in the subsequent need to modify the PIP (when a molecule has never been used before, for instance). With the concept of evolutionary PIP, certain types of developments, like molecules used for the first time in humans, will be given the possibility to initially present a high level clinical development plan.

The EMA will agree that this development plan will be completed and new information submitted at precise stages in the development. This will reduce administrative burden and create, where appropriate, a more agile PIP system.

2023/0131 (COD)

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

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

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

Having regard to the proposal from the European Commission,

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

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

Having regard to the opinion of the Committee of the Regions[2],

Acting in accordance with the ordinary legislative procedure,

Whereas:

(1) The Union pharmaceutical framework has enabled the authorisation of safe, efficacious and high-quality medicines in the Union, contributing to a high level of public health and a smooth functioning of the internal market of these products.

(2) The Pharmaceutical Strategy for Europe marks a turning point with the addition of further key objectives and by creating a modern framework that makes innovative and established medicinal products available to patients and healthcare systems at affordable prices, while ensuring security of supply and addressing environmental concerns.

(3) Addressing unequal patient access of medicinal products has become a key priority of the Pharmaceutical Strategy for Europe as has been highlighted by the Council and the European Parliament. Member States have called for revised mechanisms and incentives for development of medicinal products tailored to the level of unmet medical need, while ensuring patient access and availability of medicinal products in all Member States.

(4) Previous amendments to the Union pharmaceutical legislation have addressed access to medicinal products by providing for accelerated assessment for marketing authorisation applications or by allowing conditional marketing authorisation for medicinal products for unmet medical need. While these measures accelerated the authorisation of innovative and promising therapies, these medicinal products do not always reach the patient and patients in the Union still have different levels of access to medicines.

---

[1] OJ C , , p. .
[2] OJ C , , p. .

(5) The COVID-19 pandemic has spotlighted critical issues which require a reform of the Union pharmaceuticals framework to strengthen its resilience and to ensure that it serves the people under all circumstances.

(6) For the sake of clarity, it is necessary to replace Regulation (EC) No 726/2004 of the European Parliament and of the Council[3] with a new Regulation.

(7) Veterinary medicinal products are governed by Regulation (EU) No 2019/6 of the European Parliament and of the Council[4]. These medicinal products are outside the scope of this Regulation, even if certain provisions regarding the governance and general tasks of the Agency set out in this Regulation apply to these medicinal products. The specific tasks of the Agency in respect to veterinary medicinal products are laid down in Regulation 2019/6 and Regulation 470/2009 of the European Parliament and of the Council[5].

(8) The scope of centrally authorised medicinal products has been adapted to the realities of the market and technological development as well as the need to ensure a centralised assessment for certain categories of medicinal products. In the light of the Commission's report[6] on the experience gained, it has proved necessary to improve the operation of the marketing authorisation procedures for the placing of medicinal products on the Union market and to amend certain administrative aspects of the European Medicines Agency. In addition, the regulatory framework should be adapted to the current market conditions and economic reality, while continuing to safeguard a high level of protection of public health and the environment. The conclusions of that report call for corrections to some of the operating procedures and require adaptations to take account of scientific and technological development. It also emerges from the report that the general principles previously established which govern the centralised marketing authorisation procedure ('centralised procedure') should be maintained.

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

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

---

3 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

4 Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (OJ L 4, 7.1.2019, p. 43).

5 Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council (OJ L 152, 16.6.2009, p. 1).

6 Report from the Commission to the European Parliament and the Council on the experience acquired with the procedures for authorising and supervising medicinal products for human use, in accordance with the requirements set out in the EU legislation on medicinal products for human use, COM(2021)497 final.

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

(12) The structure and operation of the various bodies making up the Agency should be designed in such a way as to take into account the need to constantly renew scientific expertise, the need for cooperation between Union and national bodies, the need for adequate involvement of civil society, and the future enlargement of the Union. The various bodies of the Agency should establish and develop appropriate contacts with the parties concerned, in particular with representatives of patients and healthcare professionals.

(13) The chief task of the Agency should be to provide Union institutions and Member States with the best possible scientific opinions to enable them to exercise the powers of authorisation and supervision of medicinal products conferred on them by Union legal acts in the field of medicinal products. Marketing authorisation should be granted by the Commission only after a single scientific evaluation procedure addressing the quality, safety and efficacy of high-technology medicinal products has been conducted by the Agency, applying the highest possible standards.

(14) To ensure close cooperation between the Agency and scientists operating in Member States, the composition of the Management Board should be such as to guarantee that the competent authorities of the Member States are closely involved in the overall management of the Union system for authorising medicinal products.

(15) The Agency's budget should be composed of fees and charges paid by the private sector and contributions from the Union budget to implement Union policies and contributions paid from third countries.

(16) Exclusive responsibility for preparing the Agency's opinions on all questions concerning medicinal products for human use should be vested in the Committee for Medicinal Products for Human Use.

(17) The creation of the Agency through Council Regulation (EEC) No 2309/93[7] which was replaced by Regulation (EC) No 726/2004 has made it possible to reinforce the scientific evaluation and monitoring of medicinal products in the Union, in particular through its scientific bodies and committees for which competent authorities of the Member States provide experts and expertise, ensuring a high quality and independent assessment. This

[7] Council Regulation (EEC) No 1647/2003 of 18 June 2003 amending Regulation (EEC) No 2309/93 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the evaluation of Medicinal Products (OJ L 245, 29.9.2003, p. 19).

Regulation does not establish a new Agency. The Agency mentioned in this Regulation is the Agency established by Regulation (EC) No 726/2004.

(18) The field of activity of the scientific committees should be enlarged and their operating methods and composition modernised. In this regard it is important to ensure patient and healthcare professional representation in the Committee for Human Medicinal Products as it is the main evaluation committee of the Agency for medicinal products for human use.

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

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

(21) In order to allow for advice that is more informative and an exchange of information between different bodies, scientific advice provided by the Agency should sometimes take place in parallel to scientific advice provided by other bodies. This should be the case for the joint scientific consultation carried out by the Member State Coordination Group on Health Technology Assessment foreseen in Regulation (EU) 2021/2282 of the European Parliament and of the Council[8] and, in cases of medicinal products involving a medical device, the consultation of the expert panels as described in Article 106 of Regulation (EU) No 2017/745 of the European Parliament and of the Council[9]. Where parallel scientific advice consultation mechanisms are established under other relevant Union legal acts, a similar mechanism should apply.

(22) It is also necessary to reinforce the role of the scientific committees in such a way as to enable the Agency to participate actively in international scientific dialogue and to develop certain activities that will be necessary, in particular regarding international scientific harmonisation and technical cooperation with the World Health Organization.

(23) Furthermore, without prejudice to the provisions laid down in Regulation (EU) 2019/6, which remain applicable for veterinary medicinal products, in order to create greater legal certainty, it is necessary to define the responsibilities regarding the transparency rules for the Agency's work, to set certain conditions for the marketing of medicinal products authorised by the Union, to confer on the Agency powers to monitor the distribution of medicinal products authorised by the Union, to carry out inspections together with the Member States in third countries, and to specify the sanctions and the procedures for implementing them in the event of failure to observe the provisions of this Regulation and the conditions contained in the marketing authorisations granted under the procedures it establishes.

(24) In particular, the Agency should be empowered and given the capacity to carry out inspections, where this is in the interest of the Union and where the competent authorities of the Member States request support in carrying out their tasks under revised Directive 2001/83/EC of the European Parliament and of the Council[10]. The interest of the Union may

---

8 Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU (OJ L 458, 22.12.2021, p. 1).

9 Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p. 1).

10 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

concern situations where, to ensure faster access to medicinal products, challenges with inspections capacities at national level have to be addressed in a timely manner or where a response to a public health emergency or a major event requires immediate action. Providing the Agency with appropriate inspection capacity will also, in the interest of the Union, facilitate the dissemination of best practices, know-how, and improve the oversight of manufacturing of medicinal products worldwide. Following the request from a competent authority of the Member State, the Agency, at its own discretion, can accept to either provide support to the inspections of sites located in the Union or to carry out inspections of sites located in third countries.

(25) In certain cases, shortcomings in Member States' system of supervision and related enforcement activities could risk to substantially hinder the achievement of the objectives of this Regulation and those of revised Directive 2001/83/EC which could even lead to the emergence of risks to public health. To address these challenges, harmonised inspection standards should be ensured through the establishment of a joint audit programme within the Agency. This joint audit programme will also further harmonise the interpretation of good manufacturing and distribution practices on the basis of Union legislative requirements. Moreover, it will support further mutual recognition of inspection outcomes between Member States and with strategic partners. Within the joint audit programme, the competent authorities are subject to regular audits conducted by other Member States to maintain an equivalent and harmonised quality system and to ensure an appropriate implementation of relevant good manufacturing and distribution practices into national laws and equivalence with other EEA inspectorates.

(26) An inspection working group, which provides input and recommendations on all matters relating, directly or indirectly, to good manufacturing practice and good distribution practice irrespective of the marketing authorisation procedure through different reporting lines, should be established within the Agency. In particular, that working group should be responsible for the establishment, development and overall supervision of the joint audit programme.

(27) To promote innovation and the development of new medicinal products by SMEs within the meaning of Commission Recommendation 2003/361/EC[11], and to reduce the cost of the placing on the market of medicinal products for human use authorised via the centralised procedure, these undertakings should benefit from a support scheme from the Agency.

(28) The support scheme should be composed of regulatory, procedural and administrative support, and of a reduction, deferral or waiver of fees. The scheme should cover the various steps involved in pre-authorisation procedures, such as scientific advice, the submission of the marketing authorisation application, and post-authorisation procedures.

(29) Legal entities that are not engaged in an economic activity such as universities, public bodies, research centres or not-for-profit organisations, represent an important source of innovation and should also benefit from this support scheme. Whereas it should be possible to take account of the particular situation of these entities on an individual basis, such support can best be achieved by means of a dedicated support scheme, including administrative support and through the reduction, deferral and waiver of fees.

(30) The Agency should be empowered to give scientific recommendations on whether a product under development, which could potentially fall under the mandatory scope of the

[11] Commission Recommendation of 6 May 2003 concerning the definition of micro, small and medium-sized enterprises (OJ L 124, 20.5.2003, p. 36).

centralised procedure, meets the scientific criteria to be a medicinal product. Such an advisory mechanism would address, as early as possible, questions related to borderline cases with other areas such as substances of human origin, cosmetics or medical devices, which may arise as science develops. To ensure that recommendations given by the Agency take into account the views of equivalent advisory mechanisms in other legal frameworks, the Agency should consult the relevant advisory or regulatory bodies.

(31) To increase transparency of scientific assessments and all other activities, a European medicines web-portal should be created and maintained by the Agency.

(32) Experience with the functioning of the regulatory system has shown that the existing European Medicines Agency multi-scientific committee structure often creates complexity in the scientific assessment process among committees, duplication of work and non-optimised use of expertise and resources. In addition, the Agency and the competent authorities of the Member States are confronted with challenges related to limited capacity and appropriate expertise to deal with increasing number of procedures related to existing medicinal products and assessment of new ones, in particular cutting edge innovative and complex medicinal products.

(33) To optimise the functioning and efficiency of the regulatory system, the structure of the Agency's scientific committees is simplified and reduced to two main Committees for medicinal products for human use, the Committee for Medicinal Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC).

(34) The simplification of procedures should not have an impact on standards or the quality of scientific evaluation of the medicinal products to guarantee the quality, safety and efficacy of medicinal products. It should also allow for the reduction of the scientific evaluation period from 210 days to 180 days.

(35) The Agency's scientific committees should be able to delegate some of their evaluation duties to working parties which should be open to experts from the scientific world and appointed for this purpose, whilst retaining complete responsibility for the scientific opinions issued by them.

(36) The expertise of the Committee for Advanced Therapies (CAT), the Committee for Orphan Medicinal Products (COMP), the Paediatric Committee (PDCO) and Committee for Herbal Medicinal Products (HMPC) is retained through working groups, working parties and a pool of experts who are organised based on different domains and who are giving input to the CHMP and PRAC. The CHMP and PRAC consists of experts from all Member States while working parties consist in majority of experts appointed by the Member States, based on their expertise, and of external experts. The model of rapporteurs remains unchanged. Representation of patients and health care professionals, with expertise in all areas, including rare and paediatric diseases, is increased at the CHMP and PRAC, in addition to the dedicated working groups representing patients and health care professionals.

(37) Scientific committees like the CAT have been instrumental to ensure expertise and capacity building in an emerging technological field. However, after more than 15 years, advanced therapy medicinal products are now more common. The full integration of their assessment in the work of the CHMP will facilitate the assessment of medicinal products within the same therapeutic class, independent of the technology on which they are based. It will also ensure that all biological medicinal products are assessed by the same committee.

(38) To allow for more informative advice on clinical trial applications and therefore a more integrated development advice in view of future data requirements for marketing authorisation applications, the Agency can engage in consultation with representatives from

Member States with clinical trial expertise. Nevertheless, decisions on clinical trial applications should remain within the competence of the Member States, in accordance with Regulation (EU) No 536/2014 of the European Parliament and of the Council[12].

(39) To allow for a more informative decision making and for exchange of information and pooling of knowledge on general issues of scientific or technical nature related to the tasks of the Agency regarding medicinal products for human use, in particular to scientific guidelines on unmet medical needs and the design of clinical trials, or other studies and the generation of evidence along the life cycle of medicinal product, the Agency should be able to have recourse to a consultation process of authorities or bodies active along the life cycle of medicinal products. These authorities could be, as appropriate, representatives from Heads of Medicines Agencies, the Clinical Trial Coordination and Advisory Group, the SoHO Coordination Board, the Coordination Group on Health Technology Assessment, Medical Devices Coordination Group, medical devices national competent authorities, national competent authorities for pricing and reimbursement of medicines, national insurance funds or healthcare payers. The Agency should also be able to extend the consultation mechanism to consumers, patients, healthcare professionals, industry, associations representing payers, or other stakeholders, as relevant.

(40) Member States should ensure adequate funding of competent authorities to carry out their tasks under this Regulation and under [revised Directive 2001/83/EC]. In addition, in line with the Joint Statement of the European Parliament, the Council of the EU and the European Commission on decentralised agencies[13], Member States should ensure adequate resources are assigned by the competent authorities of the Member States for the purpose of their contributions to the work of the Agency, taking into account the cost-based remuneration they receive from the Agency.

(41) In the context of cooperation with international organisations to support global public health, it is important to leverage the scientific assessment performed by the Union and to promote reliance by third country regulatory authorities based on the use of certificates of medicinal products for authorised medicinal products in the Union. An applicant may request independently or as part of an application under the centralised procedure a scientific opinion from the Agency for the use of the medicinal product for markets outside the Union. The Agency should cooperate with the World Health Organization and relevant third country regulatory authorities and bodies to issue such scientific opinions.

(42) The Agency may cooperate with competent authorities of third countries in the context of performing its tasks. Such regulatory cooperation should be coherent with the broader economic relationship of the Union with the third country concerned, taking account of the relevant international agreements between the Union and that third country.

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

(44) The quality, safety and efficacy criteria of [revised Directive 2001/83/EC] should apply to medicinal products authorised by the Union under the centralised procedure. The benefit-

---

12 Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (OJ L 158, 27.5.2014, p. 1).

13 https://europa.eu/european-union/sites/europaeu/files/docs/body/joint_statement_and_common_approach_2012_en.pdf

risk balance of all medicinal products will be assessed when they are placed on the market, and at any other time the competent authority deems appropriate.

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

(46) Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes[14] lays down provisions on the protection of animals used for scientific purposes based on the principles of replacement, reduction and refinement. Any study involving the use of live animals, which provides essential information on the quality, safety and efficacy of a medicinal product, should take into account those principles of replacement, reduction and refinement, where they concern the care and use of live animals for scientific purposes, and should be optimised in order to provide the most satisfactory results whilst using the minimum number of animals. The procedures of such testing should be designed to avoid causing pain, suffering, distress or lasting harm to animals and should follow the available Agency and the International Committee for Harmonisation (ICH) guidelines. In particular, the marketing authorisation applicant and the marketing authorisation holder should take into account the principles laid down in Directive 2010/63/EU, including, where possible, use of new approach methodologies in place of animal testing. These can include but are not limited to: in vitro models, such as microphysiological systems including organ-on-chips, (2D and 3D) cell culture models, organoids and human stem cells-based models; in silico tools or read-across models.

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

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

(49) Due to the need to reduce overall approval times for medicinal products, the time between the opinion of the Committee for Medicinal Products for Human Use (CHMP) and the final

[14] Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (OJ L 276, 20.10.2010, p. 33).

decision on the application for a marketing authorisation should in principle be no longer than 46 days.

(50) On the basis of the opinion of the Agency the Commission should adopt a decision on the application by means of implementing acts. In justified cases, the Commission may return the opinion for further examination or deviate in its decision from the opinion of the Agency. Taking into account the need to make medicinal products swiftly available to patients, it should be acknowledged that the chairperson of the Standing Committee on Medicinal Products for human use will use the available mechanisms under Regulation (EU) 182/2011 of the European Parliament and of the Council[15] and notably the possibility to obtain the committee's opinion by written procedure and within expeditious deadlines which, in principle, will not exceed 10 calendar days.

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

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

(53) Environmental risks may arise from medicinal products containing or consisting of genetically modified organisms. It is thus necessary to subject such medicinal products to an environmental risk-assessment procedure similar to the procedure under Directive 2001/18/EC of the European Parliament and of the Council[16], to be conducted in parallel with the evaluation, under a single Union procedure, of the quality, safety and efficacy of the medicinal product concerned. The environmental risk-assessment should be conducted in accordance with the requirements set out in this Regulation and in [revised Directive 2001/83/EC] which are based on the principles set out in Directive 2001/18/EC but taking into account the specificities of medicinal products.

(54) [revised Directive 2001/83/EC] permits Member States to temporarily allow the use and supply of unauthorised medicinal products for public health reasons or individual patient needs and that includes medicinal products to be authorised under this Regulation. It is also necessary, that Member States are allowed under this Regulation to make a medicinal product available for compassionate use prior to its marketing authorisation. In those exceptional and urgent situations, where there is a lack of a suitable authorised medicinal product, the need to protect public health or the health of individual patients must prevail over other considerations, in particular the need to obtain a marketing authorisation and consequently, to have available complete information about the risks posed by the medicinal product, including any risks to the environment from medicinal products containing or consisting of genetically modified organisms (GMOs). To avoid delays in making these

---

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

[16] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC (OJ L 106, 17.4.2001, p. 1).

products available or uncertainties as regards their status in certain Member States, it is appropriate, in those exceptional and urgent situations, that for a medicinal product containing or consisting of GMOs, an environmental risk assessment or consent in accordance with Directive 2001/18/EC or Directive 2009/41/EC of the European Parliament and of the Council[17] should not be a prerequisite. Nevertheless, in these cases, Member States should implement appropriate measures to minimise foreseeable negative environmental impacts resulting from the intended or unintended release of the medicinal products containing or consisting of GMOs into the environment.

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

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

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

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

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

(60) Regulatory decision-making on the development, authorisation and supervision of medicinal products may be supported by access and analysis of health data, including real world data, where appropriate, i.e. health data generated outside of clinical studies. The Agency should be able to use such data, including via the Data Analysis and Real World Interrogation Network (DARWIN) and the European Health Data Space interoperable infrastructure.

---

[17] 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).

Through these capabilities the Agency may take advantage of all the potential of supercomputing, artificial intelligence and big data science to fulfil its mandate, without compromising privacy rights. Where necessary the Agency may cooperate with the competent authorities of the Member States towards this objective.

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

(62) Due to the sensitive nature of health data, the Agency should safeguard its processing operations and ensure that they respect the data protection principles of lawfulness, fairness and transparency, purpose limitation, data minimisation, accuracy, storage limitation, integrity and confidentiality. Where the processing of personal data is necessary for the purposes of this Regulation, such processing should be done in accordance with Union law on the protection of personal data. Any processing of personal data under this Regulation should take place in accordance with Regulation (EU) 2016/679[18] and Regulation (EU) 2018/1725[19] of the European Parliament and of the Council.

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

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

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

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

---

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

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

medicinal products when they fulfil the criteria for the scheme, and allow the Agency, in consultation with the Member States and the Commission, to establish selection criteria for promising medicinal products.

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

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

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

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

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

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

(73) To optimise the use of resources for both applicants for marketing authorisations and competent authorities assessing such applications, a single assessment of an active substance master file should be introduced. The outcome of the assessment should be issued through a

certificate. To avoid duplication of assessment, the use of an active substance master file certificate should be mandatory for subsequent applications or marketing authorisations for medicinal products for human use containing that active substance from an active substance master file certification holder. The Commission should be empowered to establish the procedure for the single assessment of an active substance master file. To further optimise the use of resources, the Commission should be empowered to extend the certification scheme to additional quality master files, e.g. in case of novel excipients, adjuvants, radiopharmaceutical precursors and active substance intermediates, when the intermediate is a chemical active substance by itself or used in conjugation with a biological substance.

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

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

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

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

(78) To be considered a ‘priority antimicrobial’, a medicinal product should represent a real advancement against antimicrobial resistance and should therefore bring forward non-clinical and clinical data that underpin a significant clinical benefit with respect to antimicrobial resistance. When assessing the conditions for antibiotics, the Agency shall take into account the prioritisation of pathogens as regards the risk of antimicrobial resistance provided for in the ‘WHO priority pathogens list for R&D of new antibiotics’, specifically those listed as priority 1 (critical) or priority 2 (high) or in case there is an equivalent list of priority pathogens adopted at Union level, the Agency should take such Union list into account as a priority.

(79) The creation of a voucher rewarding the development of priority antimicrobials through an additional year of regulatory data protection has the capacity to provide the needed financial

support to developers of priority antimicrobials. However, in order to ensure that the financial reward which is ultimately borne by health systems is mostly absorbed by the developer of the priority antimicrobial and not the buyer of the voucher, the number of available vouchers on the market should be kept to a minimum. It is therefore necessary to establish strict conditions of granting, transfer and use of the voucher and to further give the possibility to the Commission to revoke the voucher under certain circumstances.

(80) A transferable data exclusivity voucher should only be available to those antimicrobial products that bring a significant clinical benefit with respect to antimicrobial resistance, and which have the characteristics described in this Regulation. It is also necessary to ensure that an undertaking which receives this incentive is in turn capable to supply the medicinal product to patients across the Union in sufficient quantities and to provide information on all funding received for research related to its development in order to provide a full account of the direct financial support given to the medicinal product.

(81) To ensure a high level of transparency and complete information on the economic effect of the transferable data exclusivity voucher, notably as regards the risk of overcompensation of investment, a developer of a priority antimicrobial is required to provide information on all direct financial support received for research related to the development of the priority antimicrobial. The declaration should include direct financial support received from any source worldwide.

(82) A transfer of a voucher for a priority antimicrobial may be conducted by sale. The value of the transaction which may be monetary or otherwise agreed between the buyer and the seller, shall be made public so as to inform regulators and the public. The identity of the holder of a voucher that has been granted and not yet used should be publicly known at all times so as to ensure a maximum level of transparency and trust.

(83) The provisions related to transferable data exclusivity vouchers shall be applicable for a specified period from the entry into force of this Regulation or until a maximum number of vouchers are granted by the Commission in order to limit the total cost of the measure to Member State health systems. The limited application of the measure will also provide the possibility to assess the effect of the measure in addressing the market failure in the development of new antimicrobials addressing antimicrobial resistance and assess the cost on national health systems. Such assessment will provide the necessary knowledge to decide whether to extend the application of the measure.

(84) The period of application of the provisions on transferable exclusivity vouchers for priority antimicrobials and the total number of vouchers may be extended by the Parliament and the Council upon proposal by the Commission on the basis of the experience acquired.

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

(86) Medicinal products for rare diseases and for children should be subject to the same provisions as any other medicinal product concerning their quality, safety and efficacy, for example for what concerns the marketing authorisation procedures, the pharmacovigilance and quality requirements. However, specific requirements also apply to them. Such requirements, which are currently defined in separate legislations, should be integrated in this Regulation in order to ensure clarity and coherency of all the measures applicable to these medicinal products.

(87) Some orphan conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition cannot be recovered by the expected sales of the medicinal product. However, patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is therefore necessary to stimulate the research, development and placing on the market of appropriate medications by the pharmaceutical industry.

(88) Regulation (EC) No 141/2000 of the European Parliament and of the Council[20] has proved to be successful in boosting developments of orphan medicinal products in the Union; therefore an action at Union level remains preferable to uncoordinated measures by the Member States which may result in distortions of competition and barriers to intra-Union trade.

(89) The open and transparent Union procedure for the designation of potential medicinal products as orphan medicinal products established by Regulation (EC) No 141/2000 should be maintained. To increase legal clarity and simplification, the specific legal provisions applicable to these medicinal products should be integrated in this Regulation.

(90) Objective criteria for the orphan designation based on the prevalence of the life-threatening or chronically debilitating condition for which diagnosis, prevention or treatment is sought and the existence of no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Union should be maintained; a prevalence of not more than five affected persons per 10 000 is generally regarded as the appropriate threshold. The orphan designation criterion on the basis of return on investment has been abolished, since it has never been used.

(91) The criterion for orphan designation based on prevalence of a disease may, however, not be appropriate to identify rare diseases in all cases. For example, for conditions which have a short duration and high mortality, measuring the number of people that acquired the disease during a specific time period would better reflect if it is rare within the meaning of this Regulation than measuring the number of people who are 'affected by it' in a specific moment of time. With the aim to better identify only those diseases which are rare, the Commission should be empowered to set up specific designation criteria for certain conditions if the one provided for are not appropriate due to scientific reasons and on the basis of a recommendation of the Agency.

(92) With the aim to better identify only those diseases which are rare, the Commission should be empowered to supplement the designation criteria by a delegated act if they are not appropriate for certain conditions due to scientific reasons and on the recommendation of the Agency. In addition, the designation criteria require implementing measures to be adopted by the Commission.

(93) If a satisfactory method of diagnosis, prevention or treatment of the condition in question has already been authorised in the Union, the orphan medicinal product will have to be of significant benefit to those affected by that condition. In this context, a medicinal product authorised in one Member State is generally deemed as being authorised in the Union. It is not necessary for it to have Union authorisation or to be authorised in all Member States to be considered as a satisfactory method. In addition, commonly used methods of diagnosis, prevention or treatment that are not subject to a marketing authorisation may be considered satisfactory if there is scientific evidence of their efficacy and safety. In certain cases,

[20] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p. 1).

medicinal products prepared for an individual patient in a pharmacy according to a medical prescription, or according to the prescriptions of a pharmacopoeia and intended to be supplied directly to patients served by the pharmacy, may be considered as satisfactory treatment if they are well known and safe and this is a general practice for the relevant patient population in the Union.

(94) The competence to designate a medicinal product as an orphan medicinal product, in the form of a decision, is accorded to the Agency. This is expected to facilitate and expedite the designation procedure, while ensuring high level of scientific expertise.

(95) In order to incite faster authorisation of designated orphan medicinal products, the validity of orphan designation has been set at seven years, with the possibility of extension by the Agency under certain specified conditions; the orphan designation may be withdrawn at the request of the orphan medicine sponsor.

(96) The Agency is responsible for designation of an orphan medicinal product as well as for the setting up and management of a register of designated orphan medicinal products. That register should be publicly available and the minimum data which should be included in the register have been specified in this Regulation with the empowerment for the Commission to amend or supplement this data by a delegated act.

(97) Sponsors of orphan medicinal products designated under this Regulation should be entitled to the full benefit of incentives granted by the Union or by the Member States to support the research and development of medicinal products for the diagnosis, prevention or treatment of such conditions, including rare diseases.

(98) Patients suffering from orphan conditions deserve medicinal products of the same quality, safety and efficacy as other patients; orphan medicinal products should therefore be submitted to the normal evaluation process carried out by the Committee of Medicinal Products for Human Use for the applicant to obtain an marketing authorisation for orphan medicinal product, while a separate marketing authorisation may be granted for indications not fulfilling the criteria of an orphan medicinal product.

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

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

(101) Experience since the adoption of Regulation (EC) No 141/2000 shows that the strongest incentive for industry to invest in the development and making available of orphan medicinal products is where there is a prospect of obtaining market exclusivity for a certain number of years during which part of the investment might be recovered. In addition to the periods of market exclusivity, orphan medicinal products will benefit from the periods of regulatory protection set out in [revised Directive 2001/83/EC], including the prolongations of regulatory data protection. However, where an orphan medicinal product obtains an additional therapeutic indication it will benefit only from the prolongation of market exclusivity.(102) In order to incentivise research and development of orphan medicinal products addressing high unmet needs, to ensure market predictability and to ensure a fair

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

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

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

(105) This Regulation includes several provisions aimed to avoid not-justified benefits being derived from the market exclusivity and to improve accessibility of medicinal products by ensuring faster entry of generics and biosimilars, and similar medicinal products on the market. It also clarifies the concurrence of market exclusivity with data protection and defines situations when a similar medicinal product may be granted a marketing authorisation, despite the ongoing market exclusivity.

(106) Before a medicinal product for human use is placed on the market in one or more Member States, it has to have undergone extensive studies, including non-clinical tests and clinical trials, to ensure that it is safe, of high quality and effective for use in the target population. It is important that such studies are undertaken also on the paediatric population in order to ensure that medicinal products are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric population. It is also important that medicinal products are presented in dosages and formulations adequate for the use in children.

(107) Therefore, the development of medicinal products that could potentially be used for the paediatric population should become an integral part of the development of medicinal products, integrated into the development programme for adults. Thus, paediatric investigation plans should be submitted early during medicinal product development, in time for studies to be conducted in the paediatric population, where appropriate, before marketing authorisation applications are submitted.

(108) As the development of medicinal products is a dynamic process dependent on the result of ongoing studies, in certain cases, for example when limited information on the medicinal products are available because the medicinal products are tested for the first time in the paediatric population, a specific procedure allowing to progressively build up a paediatric investigation plan should be put in place.

(109) During public health emergencies, in order not to delay a prompt authorisation of a medicinal product intended for the treatment or the prevention of a condition related to the public health emergency, there should be a possibility to temporarily waive the requirements concerning paediatric studies to be submitted at the moment of marketing authorisation.

(110) In order to not endanger the health of children and avoid to expose them to unnecessary clinical trials, the obligation to agree and conduct paediatric studies in children should be waived when the medicinal product is likely to be ineffective or unsafe in part or all of the paediatric population, the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for children or the disease for which the medicinal product is intended occurs only in adult populations. Nevertheless, in the last

case, if on the basis of existing scientific evidence, the medicinal product due to its molecular mechanism of action is expected to be effective against a different disease in children, the obligation should be maintained.

(111) To ensure that research in the paediatric population is only conducted to meet their therapeutic needs, the Agency should agree and make public lists of waivers for medicinal products and for specific medicinal products or for classes or part of classes of medicinal products. As knowledge of science and medicine evolves over time, provision should be made for the lists of waivers to be amended. However, if a waiver is revoked, that requirement should not apply for a given period in order to allow time for at least a paediatric investigation plan to be agreed and studies in the paediatric population to be initiated before an application for marketing authorisation is submitted.

(112) With a view to ensuring that research is conducted only when safe and ethical and that the requirement for study data in the paediatric population does not block or delay the authorisation of medicinal products for other populations, the Agency may defer the initiation or completion of some or all of the measures contained in a paediatric investigation plan for a limited period of time. Such deferral should be extended only in duly justified cases.

(113) The possibility to modify an agreed paediatric investigation plan should be foreseen when the applicant encounters such difficulties with its implementation as to render the plan unworkable or no longer appropriate.

(114) The Agency, after consultation of the Commission and of interested parties, should draw up the details of the content of an application for agreement of a paediatric investigation plan, for its modification, for waivers and for deferral requests.

(115) For medicinal products intended to be developed for use only in children which would be developed independently from the current provisions, simplified details of the paediatric investigation plan should be required.

(116) To ensure that the data supporting the marketing authorisation concerning the use of a medicinal product in children to be authorised under this Regulation have been correctly developed, the Committee for Medicinal Products for Human Use should check compliance with the agreed paediatric investigation plan and any waivers and deferrals at the validation step for marketing authorisation applications.

(117) Free scientific advice should be provided by the Agency as an incentive to sponsors developing medicinal products for the paediatric population.

(118) To provide healthcare professionals and patients with information on the safe and effective use of medicinal products in the paediatric population, the results of the studies conducted in accordance with a paediatric investigation plan, independently from the fact that they support or not the use of the medicinal product in children, should be included in the summary of product characteristics and, if appropriate, in the package leaflet.

(119) To sustain the development of novel, paediatric only indications from authorised medicinal products no longer covered by intellectual property rights, it is necessary to establish a specific type of marketing authorisation, the Paediatric Use Marketing Authorisation. A Paediatric Use Marketing Authorisation should be granted through existing marketing authorisation procedures but should apply specifically for medicinal products developed exclusively for use in the paediatric population. It should be possible for the name of the medicinal product that has been granted a Paediatric Use Marketing Authorisation to retain the existing brand name of the corresponding medicinal product authorised for adults, in

order to capitalise on existing brand recognition, while benefiting from the regulatory protection associated with a new marketing authorisation.

(120) An application for a Paediatric Use Marketing Authorisation should include the submission of data concerning use of the medicinal product in the paediatric population, collected in accordance with an agreed paediatric investigation plan. These data may be derived from the published literature or from new studies. An application for a Paediatric Use Marketing Authorisation should also be able to refer to data contained in the dossier of a medicinal product which is or has been authorised in the Union. This is intended to provide an additional incentive to encourage SMEs, including generic companies, to develop off-patent medicinal products for the paediatric population.

(121) Some paediatric investigation plans may be discontinued due to various reasons despite possible positive results for the treatment of children obtained from the studies already conducted. The information of such discontinuations and their reasons should be collected by the Agency and made public in order to inform eventual third parties who may be interested in continuing the above-mentioned studies.

(122) To increase the transparency on clinical trials conducted in children in third countries and referred to in a paediatric investigation plan or conducted from a marketing authorisation holder independently from a paediatric investigation plan, information on these clinical trials should be included in the European clinical trial database created by Regulation (EU) No 536/2014.

(123) The summary of the results of all the paediatric clinical trials included in the European clinical trial database created by Regulation (EU) No 536/2014 should be made publicly available within 6 months after the end of the clinical trials unless this is not possible for justified scientific reasons.

(124) To discuss priority in medicinal product development, in particular in areas of unmet medical need for children and to coordinate studies relating to paediatric medicinal products, the Agency should set up a European network composed of patient representatives, academics, medicines developers, investigators and research centres based in the Union or in the European Economic Area.

(125) Union funding should be provided to cover all aspects of the work of the Agency resulting from paediatric related activities, such as the assessment of paediatric investigation plans, fee waivers for scientific advice, and information and transparency measures, including the database of paediatric studies and the network.

(126) It is necessary to take measures for the supervision of medicinal products authorised by the Union, and in particular for the intensive supervision of undesirable effects of these medicinal products within the framework of Union pharmacovigilance activities, so as to ensure the rapid withdrawal from the market of any medicinal product presenting a negative benefit-risk balance under normal conditions of use.

(127) The main tasks of the Agency in the area of pharmacovigilance laid down in Regulation (EC) No 726/2004 should be maintained. This includes the management of the Union pharmacovigilance database and data-processing network (the 'Eudravigilance database'), the coordination of safety announcements by the Member States and the provision to the public of information regarding safety issues. The Eudravigilance database should be the single point of receipt of pharmacovigilance information. Member States should therefore not impose any additional reporting requirements on marketing authorisation holders. The database should be fully and permanently accessible to the Member States, the Agency and

the Commission, and accessible to an appropriate extent to marketing authorisation holders and the public.

(128) To enhance the efficiency of market surveillance, the Agency should be responsible for coordinating Member States' pharmacovigilance activities. A number of provisions are required to put in place stringent and efficient pharmacovigilance procedures, to allow the competent authority of the Member State to take provisional emergency measures, including the introduction of amendments to the marketing authorisation and, finally, to permit a reassessment to be made at any time of the risk-benefit balance of a medicinal product.

(129) Scientific and technological progresses in data analytics and data infrastructure are essential for the development, authorisation and supervision of medicinal products. The digital transformation has affected regulatory decision-making, making it more data-driven and multiplying the possibilities to access evidence, across the life cycle of a medicinal product. This Regulation recognises the Agency's experience and capacity to access and analyse data submitted independently from the marketing authorisation applicant or marketing authorisation holder. On this basis, the Agency should take initiative to update the summary of product characteristics in case new efficacy or safety data has an impact on the benefit-risk balance of a medicinal product.

(130) It is also appropriate to entrust the Commission, in close cooperation with the Agency and after consultations with the Member States, with the task of coordinating the execution of the various supervisory responsibilities vested in the Member States, and in particular with the tasks of providing information on medicinal products and of checking the observance of good manufacturing, laboratory and clinical practices.

(131) It is necessary to provide for the coordinated implementation of Union procedures for the marketing authorisation of medicinal products, and of the marketing authorisation procedures of Member States which have already been harmonised to a considerable degree by [revised Directive 2001/83/EC].

(132) The Union and Member States have developed a scientific evidence-based process that allows competent authorities to determine the relative effectiveness of new or existing medicinal products. This process focuses specifically on the added value of a medicinal product in comparison with other new or existing health technologies However, this evaluation should not be conducted in the context of the marketing authorisation, for which it is agreed that the fundamental criteria should be retained. It is useful in this respect to allow for the possibility of gathering information on the methods used by the Member States to determine the therapeutic benefit obtained by each new medicinal product.

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

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

(135) The establishment of a regulatory sandbox should be based on a Commission Decision following a recommendation of the Agency. Such decision should be based on a detailed plan outlining the particularities of the sandbox as well as describing the products to be covered. A regulatory sandbox should be limited in duration and may be terminated at any time based on public health considerations. The learning stemming from a regulatory sandbox should inform future changes to the legal framework to fully integrate the particular innovative aspects into the medicinal product regulation. Where appropriate, adapted frameworks may be developed by the Commission on the basis of the results of a regulatory sandbox.

(136) Shortages of medicinal products represent a growing threat to public health, with potential serious risks to the health of patients in the Union and impacts on the right of patients to access appropriate medical treatment. The root causes of shortages are multifactorial, with challenges identified along the entire pharmaceutical value chain, from quality and manufacturing problems. In particular, shortages of medicinal products can result from supply chain disruptions and vulnerabilities affecting the supply of key ingredients and components. Therefore, all marketing authorisation holders should have shortage prevention plans in place, to prevent shortages. The Agency should provide guidance to marketing authorisation holders on approaches to streamline the implementation of those plans.

(137) To achieve a better security of supply for medicinal products in the internal market and to contribute thereby to a high level of public health protection, it is appropriate to approximate the rules on monitoring and reporting of actual or potential shortages of medicinal products, including the procedures and the respective roles and obligations of concerned entities in this Regulation. It is important to ensure continued supply of medicinal products, which is often taken for granted across Europe. This is especially true for the most critical medicinal products which are essential to ensure the continuity of care, the provision of quality healthcare and guarantee a high level of public health protection in Europe.

(138) The national competent authorities should be empowered to monitor shortages of medicinal products that are authorised through both national and centralised procedures, based on notifications of marketing authorisation holders. The Agency should be empowered to monitor shortages of medicinal products that are authorised through the centralised procedure, also based on notifications of marketing authorisation holders. When critical shortages are identified, both national competent authorities and the Agency should work in a coordinated manner to manage those critical shortages, whether the medicinal product concerned by the critical shortage is covered by a centralised marketing authorisation or a national marketing authorisation. Marketing authorisation holders and other relevant entities must provide the relevant information to inform the monitoring. Wholesale distributors and other persons or legal entities, including patient organisations or health care professionals, may also report a shortage of a given medicinal product marketed in the Member State concerned to the competent authority. The Executive Steering Group on Shortages and Safety of Medicinal Products (‘the Medicines Shortages Steering Group’ (MSSG)) already established within the Agency pursuant to Regulation (EU) 2022/123 of the European

Parliament and of the Council[21], should adopt a list of critical shortages of medicinal products and ensure monitoring of those shortages by the Agency. The MSSG should also adopt a list of critical medicinal products authorised in accordance with [revised Directive 2001/83/EC] or this Regulation to ensure monitoring of the supply of those products. The MSSG may provide recommendations on measures to be taken by marketing authorisation holders, the Member States, the Commission and other entities to resolve any critical shortage or to ensure the security of supply of those critical medicinal products to the market. Implementing acts can be adopted by the Commission to ensure that appropriate measures, including the establishment or maintenance of contingency stocks, are taken by marketing authorisation holders, wholesale distributors or other relevant entities.

(139) To ensure continuity of supply and availability of critical medicinal products to the market, rules on the transfer of the marketing authorisation prior to the permanent marketing cessation should be laid down. Such transfer should not be considered to be a variation.

(140) It is recognised that improved access to information contributes to public awareness, gives the public the opportunity to express its observations and enables authorities to take due account of those observations. The general public should therefore have access to information in the Union Register of medicinal products, the Eudravigilance database and the manufacturing and wholesale distribution database, after the deletion of any commercially confidential information by the competent authority. Regulation (EC) No 1049/2001 of the European Parliament and of the Council[22] gives the fullest possible effect to the right of public access to documents and lays down the general principles and limits on such access. The Agency should therefore give the widest possible access to the documents while carefully balancing the right for information with existing data protection requirements. Certain public and private interests, such as personal data and commercially confidential information, should be protected by way of exception in accordance with Regulation (EC) No 1049/2001.

(141) To ensure the enforcement of certain obligations relating to the marketing authorisation for medicinal products for human use granted in accordance with this Regulation, the Commission should be able to impose financial penalties. When assessing the responsibility for failures to comply with those obligations and imposing such penalties, it is important that means exist to address the fact that marketing authorisation holders could be part of a wider economic entity. Otherwise, there is a clear and identifiable risk that the responsibility for a failure to comply with those obligations could be evaded, which might have an impact on the ability to impose effective, proportional and dissuasive penalties. The penalties imposed should be effective, proportionate and dissuasive, having regard to the circumstances of the specific case. For the purposes of ensuring legal certainty in the conduct of the infringement procedure, it is necessary to set maximum amounts for penalties. Those maximum amounts should not be linked to the turnover of a particular medicinal product but the economic entity involved.

(142) To supplement or amend certain non-essential elements of this Regulation, the power to adopt acts in accordance with Article 290 of the Treaty on the Functioning of the European Union ('TFEU') should be delegated to the Commission in respect of determining the situations in which post-authorisation efficacy studies may be required; specifying the

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

[22] Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents (OJ L 145, 31.5.2001, p. 43).

categories of medicinal products to which a marketing authorisation subject to specific obligations could be granted and specifying the procedures and requirements for granting such a marketing authorisation and for its renewal; specifying exemptions to variation and the categories in which variations should be classified and establishing procedures for the examination of applications for variations to the terms of marketing authorisations as well as specifying conditions and procedures for cooperation with third countries and international organisations for examination of applications for such variations; establishing procedures for the examination of applications for the transfer of marketing authorisations; laying down the procedure and rules for the imposition of fines or periodic penalty payments for a failure to comply with the obligations under this Regulation as well as the conditions and methods for their collection. The Commission should be empowered to adopt supplementary measures laying down the situations in which post-authorisation efficacy studies may be required. It is of particular importance that the Commission carries out appropriate consultations during its preparatory work, including at expert level, and that those consultations be conducted in accordance with the principles laid down in the Interinstitutional Agreement between the European Parliament, the Council of the European Union and the European Commission of 13 April 2016 on Better Law-Making[23]. In particular, to ensure equal participation in the preparation of delegated acts, the European Parliament and the Council receive all documents at the same time as Member States' experts, and their experts systematically have access to meetings of Commission expert groups dealing with the preparation of delegated acts.

(143) To ensure uniform conditions for the implementation of this Regulation in relation to marketing authorisations for medicinal products for human use, implementing powers should be conferred on the Commission. The implementing powers related to the granting of centralised marketing authorisations and for suspending, revoking or withdrawing those authorisations, for granting vouchers, establishing and modifying regulatory sandboxes and decisions on the regulatory status of medicinal products should be exercised in accordance with Regulation (EU) 182/2011.

(144) Article 91 of Regulation (EU) No 536/2014 currently stipulates, amongst others, that it applies without prejudice to Directives 2001/18/EC and 2009/41/EC.

(145) Experience shows that, in clinical trials with investigational medicinal products containing or consisting of GMOs, the procedure to achieve compliance with the requirements of Directives 2001/18/EC and 2009/41/EC as regards the environmental risk assessment and consent by the competent authority of a Member State is complex and can take a significant amount of time.

(146) The complexity of that procedure increases greatly in the case of multi-centre clinical trials conducted in several Member States, as sponsors of clinical trials need to submit multiple requests for authorisation to multiple competent authorities in different Member States in parallel. In addition, national requirements and procedures for the environmental risk assessment (ERA) and written consent by competent authorities under GMO legislation vary greatly from one Member State to another as some Member States apply Directive 2001/18/EC, others apply Directive 2009/41/EC and there are Member States that apply either Directive 2009/41/EC or 2001/18/EC depending on the specific circumstances of a clinical trial. It is therefore not possible to determine a priori the national procedure that is to be followed.

[23] OJ L 123, 12.5.2016, p. 1.

(147) Consequently, it is particularly difficult to conduct multi-centre clinical trials with investigational medicinal products that contain or consist of GMOs involving several Member States.

(148) One of the objectives of Regulation (EU) No 536/2014 is that there will be a single coordinated and harmonised assessment of the clinical trial application between the involved Member States, with one country leading the coordination of the assessment (the Reporting Member State).

(149) It is therefore appropriate to envisage a centralised assessment of the ERA involving experts from the national competent authorities.

(150) Article 5 of Directive 2001/18/EC provides that the authorisation procedures for the deliberate release into the environment of GMOs and their related rules described in its Articles 6 to 11 do not apply for medicinal substances and compounds for human use if authorised by Union legal acts that fulfil the criteria listed in that Article.

(151) The requirement for the holding of authorisation of manufacturing and import of investigational medicinal products in the Union in accordance with Article 61(2), point (a), of Regulation (EU) No 536/2014 should be extended to investigational medicinal products containing or consisting of GMOs in Directive 2009/41/EC.

(152) It is thus judicious, in order to ensure an efficient functioning of Regulation (EU) No 536/2014, to define a specific authorisation procedure for the deliberate release of medicinal substances and compounds for human use containing or consisting of GMOs fulfilling the requirements of Article 5 of Directive 2001/18/EC and taking into account the specific characteristics of medicinal substances and compounds.

(153) Detailed rules concerning financial penalties for failure to comply with certain obligations laid down in this Regulation are specified in Commission Regulation (EC) No 658/2007[24]. Those rules should be maintained, but it is appropriate to consolidate them by moving their core elements and the list specifying those obligations into this Regulation, while maintaining a delegation of powers that allows the Commission to supplement this Regulation by laying down procedures for imposing such financial penalties. It is appropriate, in order to provide for legal certainty, to clarify that Commission Regulation (EC) No 2141/96[25] remains in force and continues to apply unless and until repealed. For the same reason, it should be clarified that Regulations (EC) No 2049/2005[26], No 507/2006[27],

---

[24] Commission Regulation (EC) No 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004 of the European Parliament and of the Council (OJ L 155, 15.6.2007, p. 10).

[25] Commission Regulation (EC) No 2141/96 of 7 November 1996 concerning the examination of an application for the transfer of a marketing authorization for a medicinal product falling within the scope of Council Regulation (EC) No 2309/93 (OJ L 286, 8.11.1996, p. 6).

[26] Commission Regulation (EC) No 2049/2005 of 15 December 2005 laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises (OJ L 329, 16.12.2005, p. 4).

[27] Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council (OJ L 92, 30.3.2006, p. 6).

No 658/2007 and (EC) No 1234/2008[28] remain in force and continue to apply unless and until repealed.

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

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

(156) The objective of this Regulation is to ensure the authorisation of high quality medicinal products, including for paediatric patients and patients suffering from rare diseases throughout the Union. Where this objective cannot be sufficiently achieved by the Member States but can rather, by reason of its scale, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union. In accordance with the principle of proportionality, as set out in that Article, this Regulation does not go beyond what is necessary in order to achieve that objective.

HAVE ADOPTED THIS REGULATION:

CHAPTER I
SUBJECT MATTER, SCOPE AND DEFINITIONS

Article 1

Subject matter and scope

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

This Regulation shall not affect the powers of Member States' authorities as regards setting the prices of medicinal products or their inclusion in the scope of the national health system or social security schemes on the basis of health, economic and social conditions. Member States may choose

[28] Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

from the particulars shown in the marketing authorisation those therapeutic indications and pack sizes which will be covered by their social security bodies.

Article 2

Definitions

For the purposes of this Regulation, the definitions laid down in Article 4 of [revised Directive 2001/83/EC[29]] shall apply.

The following definitions shall also apply:

(1) 'veterinary medicinal product' means a medicinal product as defined in Article 4, point (1), of Regulation (EU) 2019/6;

(2) 'designated orphan medicinal product' means a medicinal product under development which has been granted an orphan designation by a decision referred to in Article 64(4);

(3) 'orphan medicinal products' means a medicinal product which has been granted an orphan marketing authorisation referred to in Article 69;

(4) 'orphan medicine sponsor' means any legal or natural person, established in the Union, who submitted an application for or has been granted an orphan designation by a decision referred to in Article 64(4);

(5) 'similar medicinal product' means a medicinal product containing a similar active substance or substances as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication;

(6) 'similar active substance' means an identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism. In the case of advanced therapy medicinal products, for which the principal molecular structural features cannot be fully defined, the similarity between two active substances shall be assessed on the basis of the biological and functional characteristics;

(7) 'significant benefit' means a clinically relevant advantage or a major contribution to patient care of an orphan medicinal product if such an advantage or contribution benefits a substantial part of the target population;

(8) 'clinically superior' means that a medicinal product is shown to provide a significant therapeutic or diagnostic advantage above that provided by an orphan medicinal product in one or more of the following ways:

   (a) greater efficacy than an authorised medicinal orphan medicinal product in a substantial part of the target population;

   (b) greater safety than an authorised medicinal product in a substantial part of the target population;

   (c) in exceptional cases, where neither greater safety nor greater efficacy has been shown, demonstration that the medicinal product otherwise makes a major contribution to diagnosis or to patient care.

(11) 'paediatric use marketing authorisation' means a marketing authorisation granted in respect of a medicinal product for human use which is not protected by a supplementary protection

[29] [Name of revised Directive 2001/83/EC, date (OJ L XX, XX.XX.XXX, p. X).]

certificate under Regulation (EC) No 469/2009 of the European Parliament and of the Council concerning the supplementary protection certificate for medicinal products[30] [OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate, covering exclusively therapeutic indications which are relevant for use in the paediatric population, or subsets thereof, including the appropriate strength, pharmaceutical form or route of administration for that product.

(12) 'regulatory sandbox' means a regulatory framework during which it is possible to develop, validate and test in a controlled environment innovative or adapted regulatory solutions that facilitate the development and authorisation of innovative products which are likely to fall in the scope of this Regulation, pursuant to a specific plan and for a limited time under regulatory supervision.

(13) 'critical medicinal product' means a medicinal product for which insufficient supply results in serious harm or risk of serious harm to patients and identified using the methodology pursuant to Article 130(1), point (a).

(14) 'shortage' means a situation in which the supply of a medicinal product that is authorised and placed on the market in a Member State does not meet the demand for that medicinal product in that Member State.

(15) 'critical shortage in the Member State' means a shortage of a medicinal product, for which there is no appropriate alternative medicinal product available on the market in that Member State, and that shortage cannot be resolved.

(16) 'critical shortage' means a critical shortage in the Member State for which coordinated Union level action is considered necessary to resolve that shortage in accordance with this Regulation.

Article 3

Centrally authorised medicinal products

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

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

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

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

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

[30] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (OJ L 152, 16.6.2009, p. 1).

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

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

Article 4

Member State authorisation of generics of centrally authorised medicinal products

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

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

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

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

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.

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 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 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[31], 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, the Agency may, following the advice of the Committee for Medicinal Products for Human Use regarding the maturity of the data related to the development, offer to the applicant a phased review of complete data packages for individual modules of particulars and documentation as referred to in paragraph 1.

The Agency may at any stage suspend or cancel the phased review, where the Committee for Medicinal Products for Human Use considers that the submitted data are not of sufficient maturity or where it is considered that the medicinal product 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.

[31] 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).

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 25 of [revised Directive 2001/83/EC].

5. The marketing authorisation applicant shall demonstrate 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 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.

   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 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 contact with the medicinal product.

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 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. 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 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 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 uncertainty as to the surrogate endpoint relation to the expected health outcome, where appropriate and relevant for the benefit-risk balance, a post-authorisation obligation to substantiate the clinical benefit;

(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 out medicinal product-specific validation studies 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].

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;

(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. After a marketing authorisation has been granted, the marketing authorisation holder shall inform the Agency of the dates of actual marketing of the medicinal product for human use in the Member States, taking into account the various presentations authorised.

The marketing authorisation holder shall notify the Agency and the competent authority of the Member State concerned of the following:

(a) its intention to permanently cease the marketing of a medicinal product in that Member State in accordance with Article 116(1), point (a); or

(b) its intention to temporarily suspend the marketing of a medicinal product in that Member State in accordance with Article 116(1), point (c); or

(c) a potential or actual shortage in that Member State in accordance with Article 116(1), point (d); and

its reasons for such action under points (a) and (b) in accordance with Article 24, as well as any other reason relating to precautionary actions with regard to quality, safety, efficacy and the environment.

Upon request by the Agency, particularly in the context of pharmacovigilance, the marketing authorisation holder shall provide the Agency with all data relating to the volume of sales of the medicinal product at Union level, broken down by Member State, and any data in the marketing authorisation holder's possession relating to the volume of prescriptions in the Union and its Member States.

Article 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 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.

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.

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.

   Where the Agency considers that any of the post-authorisations studies referred to in points (a) to (c) 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 24

Suspension of marketing, withdrawal from the market of a medicinal product, withdrawal of a marketing authorisation by the marketing authorisation holder

1. In addition to the notification made pursuant to Article 116, the marketing authorisation holder shall notify the Agency without undue delay of any action they take to suspend the marketing of a medicinal product, to withdraw a medicinal product from the market, to request the withdrawal of a marketing authorisation or not to apply for the renewal of a marketing authorisation, together with the reasons for such action.

   The marketing authorisation holder shall declare if such action is based on the following grounds:

   (a) the medicinal product is harmful;

   (b) it lacks therapeutic efficacy;

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

   (d) its qualitative and quantitative composition is not as declared;

   (e) the controls on the medicinal product or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some

other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled; or

(f) a serious risk to the environment or to public health via the environment has been identified and not sufficiently addressed by the marketing authorisation holder.

Where the action referred to in the first subparagraph is to withdraw a medicinal product from the market, the marketing authorisation holder shall provide information on the impact of such withdrawal on patients who are already being treated.

The notification of the permanent withdrawal of a medicinal product from the market or of the temporary suspension of the marketing authorisation, or of the permanent withdrawal of a marketing authorisation or of the temporary disruption in supply of a medicinal product shall be made in accordance with Article 116(1).

2. The marketing authorisation holder shall make the notification pursuant to paragraph 1 if the action is taken in a third country and such action is based on any of the grounds set out in Articles 195 or 196(1) of [revised Directive 2001/83/EC].

3. In the cases referred to in paragraphs 1 and 2, the Agency shall forward the information to the competent authorities of the Member States without undue delay.

4. Where the marketing authorisation holder intends to permanently withdraw the marketing authorisation for a critical medicinal product, the marketing authorisation holder shall, prior to the notification referred to in paragraph 1, offer, on reasonable terms, to transfer the marketing authorisation to a third party that has declared its intention to place that critical medicinal product on the market, or to use the pharmaceutical non-clinical and clinical documentation contained in the file of the medicinal product for the purposes of submitting an application in accordance with Article 14 of [revised Directive 2001/83/EC].

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 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. 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. 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 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 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.

Article 29

Regulatory protection periods

Without prejudice to the law on the protection of industrial and commercial property, medicinal products for human use which have been authorised in accordance with this Regulation shall benefit from the periods of regulatory protection set out in Chapter VII of [revised Directive 2001/83/EC].

SECTION 3

TEMPORARY EMERGENCY MARKETING AUTHORISATION

Article 30

Temporary emergency marketing authorisation

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

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

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

Article 31

Criteria for granting a temporary emergency marketing authorisation

A temporary emergency marketing authorisation may be granted only after the recognition of a public health emergency at Union level in accordance with Article 23 of Regulation (EU) 2022/2371 of the European Parliament and of the Council[32] and where the following requirements are met:

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

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

Article 32

Scientific opinion

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

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

   The Agency shall update its scientific opinion as necessary.

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

Article 33

Commission decision for a temporary emergency marketing authorisation

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

[32] Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU (OJ L 314, 6.12.2022, p. 26).

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

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

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

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

Article 34

Validity of a temporary emergency marketing authorisation

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

Article 35

Variation, suspension or revocation of a temporary emergency marketing authorisation

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

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

(b) it is appropriate to protect public health;

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

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

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

Article 36

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

The marketing authorisation holder of an authorisation in accordance with Article 33 may submit an application in accordance with Articles 5 and 6 in order to obtain an authorisation in accordance with Articles 13, 16 or 19.

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

Article 37

Transitional period

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

Article 38

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

1. For medicinal products for which a temporary emergency marketing authorisation may be considered by the Agency, Article 18(1) and (2) of Regulation (EU) 2022/123[33] shall apply.

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

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

Article 39

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

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

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

CHAPTER III
INCENTIVES FOR THE DEVELOPMENT OF 'PRIORITY ANTIMICROBIALS'

Article 40

Granting the right to a transferable data exclusivity voucher

1. Following a request by the applicant when applying for a marketing authorisation, the Commission may, by means of implementing acts, grant a transferable data exclusivity voucher to a 'priority antimicrobial' referred to in paragraph 3, under the conditions referred to in paragraph 4 based on a scientific assessment by the Agency.

2. The voucher referred to in paragraph 1 shall give the right to its holder to an additional 12 months of data protection for one authorised medicinal product.

3. An antimicrobial shall be considered 'priority antimicrobial' if preclinical and clinical data underpin a significant clinical benefit with respect to antimicrobial resistance and it has at least one of the following characteristics:

   (a) it represents a new class of antimicrobials;

   (b) its mechanism of action is distinctly different from that of any authorised antimicrobial in the Union;

   (c) it contains an active substance not previously authorised in a medicinal product in the Union that addresses a multi-drug resistant organism and serious or life threatening infection.

   In the scientific assessment of the criteria referred to in the first subparagraph, and in the case of antibiotics, the Agency shall take into account the 'WHO priority pathogens list for R&D of new antibiotics', or an equivalent list established at Union level.

4. To be granted the voucher by the Commission, the applicant shall:

   (a) demonstrate capacity to supply the priority antimicrobial in sufficient quantities for the expected needs of the Union market;

   (b) provide information on all direct financial support received for research related to the development of the priority antimicrobial.

   Within 30 days after the marketing authorisation is granted, the marketing authorisation holder shall make the information referred to in point (b) accessible to the public via a dedicated webpage and shall communicate, in a timely manner the electronic link to that webpage to the Agency.

Article 41

Transfer and use of the voucher

1. A voucher may be used to extend the data protection for a period of 12 months of the priority antimicrobial or another medicinal product authorised in accordance with this Regulation of the same or different marketing authorisation holder.

   A voucher shall only be used once and in relation to a single centrally authorised medicinal product and only if that product is within its first four years of regulatory data protection.

A voucher may only be used if the marketing authorisation of the priority antimicrobial for which the right was initially granted has not been withdrawn.

2. To use the voucher, its owner shall apply for a variation of the marketing authorisation concerned in accordance with Article 47 to extend the data protection.

3. A voucher may be transferred to another marketing authorisation holder and shall not be transferred further.

4. A marketing authorisation holder to whom a voucher is transferred shall notify the Agency of the transfer within 30 days, stating the value of the transaction between the two parties. The Agency shall make this information publicly available.

Article 42

Validity of the voucher

1. A voucher shall cease to be valid in the following cases:

   (a) where the Commission adopts a decision in accordance with Article 47 to extend the data protection of the receiving medicinal product;

   (b) where it is not used within 5 years from the date it was granted.

2. The Commission may revoke the voucher prior to its transfer as referred to in Article 41(3) if a request for supply, procurement or purchase of the priority antimicrobial in the Union has not been fulfilled.

3. Without prejudice to patent rights, or supplementary protection certificates[34], if a priority antimicrobial is withdrawn from the Union market prior to expiry of the periods of market and data protection laid down in Articles 80 and 81 of [revised Directive 2001/83/EC], those periods shall not prevent the validation, authorisation and placing on the market of a medicinal product using the priority antimicrobial as a reference medicinal product in accordance with Chapter II, Section 2 of [revised Directive 2001/83].

Article 43

Duration of application of Chapter III

This Chapter shall apply until [*Note to OP: insert the date of 15 years after the date of entry into force of this Regulation*] or until the date when the Commission has granted a total of 10 vouchers in accordance with this Chapter, whichever date is the earliest.

CHAPTER IV
POST-MARKETING AUTHORISATION MEASURES

Article 44

Urgent safety or efficacy restrictions

1. If, in the event of a risk to public health, the marketing authorisation holder takes urgent safety or efficacy restrictions on their own initiative, the marketing authorisation holder shall immediately inform the Agency.

[34] Regulation (EC) No 469/2009 of the European Parliament and of the Council, (OJ L 152, 16.6.2009, p. 1).

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

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

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

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

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

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

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

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

Article 45

Update of a marketing authorisation related to scientific and technological developments

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

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

The marketing authorisation holder shall without undue delay inform the Agency and the Commission of any prohibition or restriction imposed on the marketing authorisation holder or any entity in contractual relationship with the marketing authorisation holder by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether

or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.

3. The marketing authorisation holder shall ensure that the product information and the terms of the marketing authorisation including the summary of product characteristics, the labelling and package leaflet are kept up to date with the current scientific knowledge including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal set-up in accordance with Article 104.

4. The Agency may at any time request the marketing authorisation holder to submit data demonstrating that the benefit-risk balance remains favourable. The marketing authorisation holder shall answer fully and promptly any such request. The marketing authorisation holder shall also respond fully and within the time limit set to any request of a competent authority regarding the implementation of any measures previously imposed, including risk minimisation measures.

   The Agency may at any time ask the marketing authorisation holder to submit a copy of the pharmacovigilance system master file. The marketing authorisation holder shall submit that copy at the latest seven days after receipt of the request.

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

Article 46

Update of risk management plans

1. The marketing authorisation holder of a medicinal product referred to in Articles 9, and 11 of [revised Directive 2001/83/EC] shall submit to the Agency a risk management plan and a summary thereof, where the marketing authorisation for the reference medicinal product is withdrawn but the marketing authorisation for the medicinal product referred to in Articles 9 and 11 of [revised Directive 2001/83/EC] is maintained.

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

2. The Agency may impose an obligation on a marketing authorisation holder for a medicinal product referred to in Articles 9, 10, 11 and 12 of [revised Directive 2001/83/EC] to submit a risk management plan and summary thereof where:

   (a) additional risk minimisation measures have been imposed concerning the reference medicinal product; or

   (b) it is justified on pharmacovigilance grounds.

3. In the case mentioned referred to in paragraph 2, point (a), the risk management plan shall be aligned with the risk management plan for the reference medicinal product.

4. The imposition of the obligation referred to in paragraph 3, shall be duly justified in writing, notified to the marketing authorisation holder and shall include the deadline for submission of the risk management plan and the summary by means of a variation in accordance with Article 47.

Article 47

Variation of marketing authorisation

1. An application for variation of a centralised marketing authorisation by the marketing authorisation holder shall be made electronically in the formats made available by the Agency, unless the variation is an update by the marketing authorisation holder of their information held in a database.

2. Variations shall be classified in different categories depending on the level of risk to public health and the potential impact on the quality, safety and efficacy of the medicinal product concerned. Those categories shall range from changes to the terms of the marketing authorisation that have the highest potential impact on the quality, safety or efficacy of the medicinal product, to changes that have no or minimal impact thereon and to administrative changes.

3. The procedures for examination of applications for variations shall be proportionate to the risk and impact involved. Those procedures shall range from procedures that allow implementation only after approval based on a complete scientific assessment to procedures that allow immediate implementation and subsequent notification by the marketing authorisation holder to the Agency. Such procedures may also include updates by the marketing authorisation holder of their information held in a database.

4. The Commission is empowered to adopt delegated acts in accordance with Article 175 to supplement this Regulation by establishing the following:

   (a) the categories referred to in paragraph 2 in which variations shall be classified;

   (b) procedures for the examination of applications for variations to the terms of marketing authorisations, including procedures for updates through a database;

   (c) the conditions for submission of a single application for more than one change to the terms of the same marketing authorisation and for the same change to the terms of several marketing authorisations;

   (d) specifying exemptions to the variation procedures where the update of information in the marketing authorisation referred to in Annex I may be directly implemented;

   (e) the conditions and procedures for cooperation with competent authorities of third countries or international organisations on examination of applications for variations to the terms of marketing authorisation.

Article 48

Scientific opinion on data submitted from not-for-profit entities for repurposing of authorised medicinal products

1. An entity not engaged in an economic activity ('not-for-profit entity') may submit to the Agency or to a competent authority of the Member State substantive non-clinical or clinical evidence for a new therapeutic indication that is expected to fulfil an unmet medical need.

   The Agency may, at the request of a Member State, the Commission, or on its own initiative and on the basis of all available evidence make a scientific evaluation of the benefit-risk of the use of a medicinal product with a new therapeutic indication that concerns an unmet medical need.

The opinion of the Agency shall be made publicly available and the competent authorities of the Member States shall be informed.

2. In cases where the opinion is favourable, marketing authorisation holders of the medicinal products concerned shall submit a variation to update the product information with the new therapeutic indication.

3. Article 81(2), point (c) of [revised Directive 2001/83/EC] shall not apply for variations under this Article.

Article 49

Transfer of marketing authorisation

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

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

Article 50

Supervisory authority

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

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

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

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

Article 51

Responsibilities of the supervisory authorities

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

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

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

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

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

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

3. Taking into account any agreements which may have been concluded between the Union and third countries in accordance with Article 50, the Commission may, following a reasoned request from a Member State or from the Committee for Medicinal Products for Human Use, or on its own initiative, require a manufacturer established in a third country to submit to an inspection.

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

Article 52

Inspection capacity of the Agency

1. When an inspection, included in the system of supervision referred to in Article 188(1), point (a) of [revised Directive 2001/83/EC] is requested, as referred to in Article 11(2), for a site located in a third country, the supervisory authority for this site may request the Agency to participate in the inspection or to carry out the inspection.

2. The Agency, following a request in accordance with paragraph 1, may decide either of the following:

(a) to lend its assistance by participating in a joint inspection with the supervisory authority of the site. In that case the supervisory authority leads the inspection and the follow up thereof. After completion of the inspection, the supervisory authority grants the relevant good manufacturing practice (GMP) certificate and enters the certificate in the Union database; or

(b) to carry out the inspection and the follow up thereof on behalf of the supervisory authority. After completion of the inspection, the Agency grants the relevant GMP certificate and enters the certificate in the Union database referred to in Article 188(15) of [revised Directive 2001/83/EC].

Where the Agency decides to carry out the inspection, the Agency may request other Member States to participate in the inspection. To any such request, the provisions on joint inspections of Article 189 of [revised Directive 2001/83/EC] shall apply. In case the Agency carries out the inspection in form of a joint inspection, the Agency leads the inspection.

The Agency may also request to be accompanied by a rapporteur or expert appointed by the Committee for Medicinal Products for Human Use.

Where a follow-up inspection is required in view of a non-compliance GMP certificate issued by the Agency, the supervisory authority of the site will be in charge of its performance; the procedure of paragraph 2 shall apply if the supervisory authority for this site requests the Agency to participate in the follow up inspection or to take over the performance of the inspection.

3. The Agency shall take into account the criteria set out in Annex III when taking its decision in accordance with paragraph 2.

4. Article 188, paragraph 6, and paragraphs 8 to 17 of [revised Directive 2001/83/EC] shall apply to the inspections referred to in paragraph 2.

The Agency's inspectors shall have the same powers conferred on official representatives of the competent authority pursuant to these provisions.

5. Following a request by a Member State, the inspectors of the Agency may provide support to such Member State when it performs inspections referred to in Article 78 of Regulation (EU) 536/2014. The Agency shall take a decision whether to carry out itself such inspection based on the criteria set out in Annex III.

6. The Agency shall ensure that

(a) appropriate resources are made available for the performance of inspection tasks in accordance with the paragraphs 2 and 5;

(b) the inspectors of the Agency possess expertise, technical knowledge, and formal qualifications equivalent to those of the national inspectors as detailed in the compilation, published by the Commission, on Union procedures on inspections and exchange of information.

(c) it participates as an inspectorate in the Joint Audit Programme and be subjected to periodic audits.

Article 53

International Inspections

1. The Agency shall in consultation with the Commission, coordinate a structured cooperation on inspections in third countries between Member States, and as relevant the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe, the World Health Organisation and trusted international authorities, by means of international inspection programmes.

2. In cooperation with the Agency, the Commission may adopt detailed guidelines laying down the principles applicable to those international inspection programmes.

Article 54

Joint Audit Programme

1. The inspection working group referred to in Article 142, point (k), shall ensure the following:

   (a) establish and develop the joint audit programme ('JAP') and supervise it;

   (b) monitor any measure taken by the Member State pursuant and limited to paragraph 4;

   (c) ensure cooperation with relevant international and Union level bodies to facilitate the work of the joint audit programme.

   For the purposes of the first subparagraph, the inspection working group may establish an operational subgroup.

2. For the purposes of paragraph 1, point (a), each Member State shall:

   (a) provide trained auditors;

   (b) accept that the competent authority in charge of the implementation of good manufacturing and good distribution practice and related surveillance and enforcement activities applicable to medicinal products and active substances are audited, regularly and where appropriate, according to the joint audit programme.

3. The joint audit programme shall be considered an integral part of the quality system of the inspectorates referred to in Article 3(3) of Commission Directive (EU) 2017/1572[35] and ensure that adequate and equivalent quality standards are maintained within the Union network of national competent authorities.

4. Under the joint audit programme, the auditors shall issue an audit report after each audit. The audit report shall include, where relevant, appropriate recommendations on measures that the Member State concerned shall consider to take to ensure that its relevant quality system and its enforcement activities are consistent with Union quality standards.

   At the request of the Member State, the Commission or the Agency may support that Member State in taking the appropriate measures pursuant to the first subparagraph.

5. For the purposes of paragraph 4, the Agency shall:

   (a) ensure the quality and consistency of the joint audit programme's audit reports;

   (b) establish the criteria for the provision of the joint audit programme's recommendations.

6. The compilation of Union procedures on inspections and exchange of information referred to in Article 3(1) of Directive 2017/1572 shall be updated by the Agency to cover rules applicable to the functioning, structure, and tasks of the joint audit programme.

7. The Union shall provide the financing for activities that support the work of the joint audit programme.

---

[35] Commission Directive (EU) 2017/1572 of 15 September 2017 supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for medicinal products for human use (OJ L 238, 16.9.2017, p. 44).

Article 55

Referral procedure

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

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

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

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

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

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

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

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

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

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

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

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

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

Article 56

Action on conditional marketing authorisation

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

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

Article 57

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

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

CHAPTER V
PRE-AUTHORISATION REGULATORY SUPPORT

Article 58

Scientific advice

1. Undertakings or, as relevant, not-for-profit entities may request scientific advice as referred to in Article 138(1), second subparagraph, point (p) , from the Agency.

   Such advice can also be requested for medicinal products referred to in Articles 83 and 84 of [revised Directive 2001/83/EC].

2. In the preparation of the scientific advice referred to in paragraph 1 and upon request by undertakings or, as relevant, not-for-profit entities that requested the scientific advice, the Agency may consult experts of the Member States with clinical trial or medical device expertise or the expert panels designated in accordance with Article 106(1) of Regulation (EU) 2017/745.

3. In the preparation of the scientific advice referred to in paragraph 1 and in duly justified cases, the Agency may consult authorities established in other Union legal acts as relevant for the provision of the scientific advice in question or other public bodies established in the Union, as applicable.

4. The Agency shall include in the European public assessment report the key areas of the scientific advice once the corresponding marketing authorisation decision has been taken in relation to the medicinal product, after deletion of any information of a commercially confidential nature.

Article 59

Parallel scientific advice

1. Undertakings or, as relevant, not-for-profit entities established in the Union may request that the scientific advice referred to in Article 58(1) takes place in parallel to the joint scientific consultation carried out by the Member State Coordination Group on Health Technology Assessment, in line with Article 16(5) of Regulation (EU) 2021/2282.

2. In case of medicinal products involving a medical device, undertakings or, as relevant, not-for-profit entities may request scientific advice as referred to in Article 58(1) in parallel with the consultation of the expert panels referred to in Article 61(2) of Regulation (EU) 2017/745.

3. In the case of paragraph 2, the scientific advice, as referred to in Article 58(1), shall involve exchanges of information between the respective authorities or bodies and, where applicable, have synchronised timing, while preserving the separation of their respective remits.

Article 60

Enhanced scientific and regulatory support for priority medicinal products ('PRIME')

1. The Agency may offer enhanced scientific and regulatory support, including as applicable consultation with other bodies as referred to in Articles 58 and 59 and accelerated assessment mechanisms, for certain medicinal products that, based on preliminary evidence submitted by the developer fulfil the following conditions:

   (a) are likely to address an unmet medical need as referred to in Article 83(1) of [revised Directive 2001/83/EC];

   (b) are orphan medicinal products and are likely to address a high unmet medical need as referred to in Article 70(1);

   (c) are expected to be of major interest from the point of view of public health, in particular as regards therapeutic innovation, taking into account the early stage of development, or antimicrobials with any of the characteristics mentioned in Article 40(3).

2. The Agency, at the request of the Commission and after consulting the EMA Emergency Task Force, may offer enhanced scientific and regulatory support to developers of a medicinal product preventing, diagnosing or treating a disease resulting from serious cross border threats to health if access to such products is considered necessary to ensure high level of Union preparedness and response to health threats.

3. The Agency may stop the enhanced support if it is established that the medicinal product will not address the identified unmet medical need to the anticipated extent.

4. The compliance of a medicinal product with the criteria set out in Article 83 of [revised Directive 2001/83/EC] shall be assessed on the basis of the relevant criteria, independently of whether it has received priority medicinal product support under this Article.

Article 61

Scientific recommendation on regulatory status

1. For products under development which may fall within the categories of medicinal products to be authorised by the Union listed in Annex I, a developer or a competent authority of the Member States may submit a duly substantiated request to the Agency for a scientific recommendation with a view to determining on scientific grounds whether the concerned product is potentially a 'medicinal product', including an 'advanced therapy medicinal product' as defined in Article 2 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council[36].

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

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

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

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

Article 62

Decision on regulatory status

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

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

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

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

---

[36] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121).

CHAPTER VI
ORPHAN MEDICINAL PRODUCTS

Article 63

Criteria for orphan designation

1. A medicinal product that is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition shall be designated as an orphan medicinal product where the orphan medicine sponsor can demonstrate that the following requirements are met:

   (a) the condition affects not more than five in 10 000 persons in the Union when the application for an orphan designation is submitted;

   (b) there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Union or, where such method exists, that the medicinal product would be of significant benefit to those affected by that condition.

2. By way of derogation from paragraph 1, point (a), and on the basis of a recommendation from the Agency, when the requirements specified in paragraph 1, point (a), are not appropriate due to the specific characteristics of certain conditions or any other scientific reasons, the Commission is empowered to adopt delegated acts in accordance with Article 175 in order to supplement paragraph 1, point (a), by setting specific criteria for certain conditions.

3. The Commission shall adopt the necessary provisions for implementing this Article by means of implementing acts in accordance with the procedure laid down in Article 173(2) in order to further specify the requirements referred to in paragraph 1.

Article 64

Granting an orphan designation

1. The orphan medicine sponsor shall submit an application for the designation of the orphan medicinal product to the Agency at any stage of the development of the medicinal product before the application for marketing authorisation referred to in Articles 5 and 6 is submitted.

2. The application of the orphan medicine sponsor shall be accompanied by the following particulars and documentation:

   (a) name or corporate name and permanent address of the orphan medicine sponsor;

   (b) active substances of the medicinal product;

   (c) proposed condition for which it is intended or the proposed therapeutic indication;

   (d) justification that the criteria laid down in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2) are fulfilled and a description of the stage of development, including the expected therapeutic indication.

   The orphan medicine sponsor shall be responsible for the accuracy of the particulars and documentation.

3. The Agency shall, in consultation with the Member States, the Commission and interested parties, draw up detailed guidelines on the required procedure, format and content of

applications for designation and for the transfer of the orphan designation pursuant to Article 65.

4. The Agency shall adopt a decision granting or refusing the orphan designation based on the criteria referred to in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2) within 90 days of the receipt of a valid application. The application is considered valid if it includes all the particulars and documentation referred to in paragraph 2.

For the purpose of establishing whether the orphan designation criteria are fulfilled, the Agency may consult the Committee for Medicinal Products for Human Use or one of its working parties referred to in Article 150(2), first subparagraph. The outcome of such consultations shall be annexed to the decision, as part of the scientific conclusions of the Agency which justify the decision.

The decision together with the Annexes referred to in this paragraph shall be notified to the applicant.

5. Decisions of the Agency on granting or refusing the orphan designation shall be made public after deletion of any information of a commercially confidential nature.

Article 65

Transfer of orphan designation

1. The orphan designation may be transferred from a current orphan medicine sponsor to a new orphan medicine sponsor. The transfer shall be subject to prior approval by the Agency, following the submission of an application for the transfer to the Agency.

2. The application of the current orphan medicine sponsor shall be accompanied by the following particulars and documentation:

(a) name or corporate name and permanent address of the current and new orphan medicine sponsor;

(b) decision on granting an orphan designation as referred to in Article 64(4);

(c) designation number as referred to in Article 67(3), point (e).

3 The Agency shall adopt a decision granting or refusing the transfer of the orphan designation within 30 days of the receipt of a valid application by the current orphan medicine sponsor. The application is considered valid if it includes all the particulars and documentation referred to in paragraph 2. The Agency shall address its decision to the current and new orphan medicine sponsor.

Article 66

Validity of orphan designation

1. An orphan designation shall be valid for seven years. During this period, the orphan medicine sponsor shall be eligible for incentives referred to in Article 68.

2. By way of derogation from paragraph 1, on the basis of a justified request of the orphan medicine sponsor, the Agency may extend the validity, where the orphan medicine sponsor can provide evidence that the relevant studies supporting the use of the designated orphan medicinal product in the applied conditions are ongoing and promising with regard to the filing of a future application. Such an extension shall be limited in time, taking into

account the expected remaining time needed to file an application for marketing authorisation.

3. By way of derogation from paragraph 1, where an orphan designation is valid at the time when a marketing authorisation for an orphan medicinal product has been submitted in accordance with Article 5, the orphan designation shall remain valid until a decision is adopted by the Commission in accordance with Article 13(2).

4. An orphan designation ceases to be valid once an orphan medicine sponsor has obtained a marketing authorisation for the relevant medicinal product in accordance with Article 13(2).

5. At any time, an orphan designation may be withdrawn at the request of the orphan medicine sponsor.

Article 67

Register of designated orphan medicinal products

1. The register of designated orphan medicinal products shall list all designated orphan medicinal products. It shall be set up and managed by the Agency and be publicly available.

2. Where an orphan designation ceases to be valid or is withdrawn pursuant to Article 66, the Agency shall make an entry in the register of designated orphan medicinal products.

3. The information on the designated orphan medicinal product entered in the register of designated orphan medicinal products shall include at least the following:

   (a) the information on the active substance;

   (b) the name and address of the orphan medicine sponsor;

   (c) the condition for which it is intended or the proposed therapeutic indication;

   (d) the designation date;

   (e) the designation number;

   (f) the decision on granting the orphan designation.

4. The Commission shall be empowered to adopt delegated acts in accordance with Article 175 in order to amend the information to be included in the register of designated orphan medicinal products referred to in paragraph 3 to ensure appropriate information of the users of that register.

Article 68

Protocol assistance and research support for orphan medicinal products

1. The orphan medicine sponsor may, prior to the submission of an application for marketing authorisation, request advice from the Agency on the following:

   (a) the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product, as referred to Article 138(1), second subparagraph, point (p);

   (b) the demonstration of significant benefit within the scope of the designated orphan indication;

(c) the demonstration of similarity to or clinical superiority over other medicinal products, which have market exclusivity for the same indication.

2. Medicinal products designated as orphan medicinal products under the provisions of this Regulation shall be eligible for incentives made available by the Union and by the Member States to support research into, and the development and availability of, orphan medicinal products and in particular aid for research for small- and medium-sized undertakings provided for in framework programmes for research and technological development.

Article 69

Orphan marketing authorisation

1. Applications for an orphan marketing authorisation shall be submitted in accordance with Articles 5 and 6 and the related marketing authorisation shall be obtained in accordance with Articles 13(2).

2. In addition, the applicant shall demonstrate that the medicinal product has been granted an orphan designation and that the criteria set out in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2) are fulfilled for the therapeutic indication sought.

   Where appropriate, the applicant shall provide relevant evidence to demonstrate that the medicinal product addresses a high unmet medical need as specified in Article 70(1).

3. The Committee for Medicinal Products for Human Use shall assess whether the medicinal product fulfils the requirements set out in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2). In the situation referred in paragraph 2, subparagraph 2, that Committee shall also assess whether the medicinal product addresses a high unmet medical need as specified in Article 70(1).

   Such assessment shall be subject to the same timelines as the application for the marketing authorisation itself and detailed conclusions of such assessment shall be part of the scientific opinion of the Committee for Medicinal Products for Human Use in accordance with Article 12(1).

   The assessment and its conclusions shall be part of the opinion referred to in Article 12(1) and, where relevant, the opinion referred to in Article 12(3).

5. The orphan marketing authorisation shall cover only those therapeutic indications, which fulfil the requirements set out in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2) at the time when the orphan marketing authorisation is granted.

6. If after the submission of an application for the orphan marketing authorisation and prior to the opinion of the Committee for Medicinal Products for Human Use the orphan designation is withdrawn in accordance with Article 66(5), the application for the orphan marketing authorisation shall be treated as the application for a marketing authorisation in accordance with Article 6.

7. An applicant may submit an application for a separate marketing authorisation for other indications which do not fulfil the requirements set out in Article 63(1) or in the relevant delegated acts adopted in accordance with Article 63(2).

Article 70

Orphan medicinal products addressing a high unmet medical need

1. An orphan medicinal product shall be considered as addressing a high unmet medical need where it fulfils the following requirements:

   (a) there is no medicinal product authorised in the Union for such condition orwhere, despite medicinal products being authorised for such condition in the Union, the applicant demonstrates that the orphan medicinal product, in addition to having a significant benefit, will bring exceptional therapeutic advancement;

   (b) the use of the orphan medicinal product results in a meaningful reduction in disease morbidity or mortality for the relevant patient population.

2. A medicinal product for which an application has been submitted in accordance with Article 13 of [revised Directive 2001/83/EC] shall not be considered as addressing a high unmet medical need.

3. Where the Agency adopts scientific guidelines for the application of this Article, it shall consult the Commission and the authorities or bodies referred to in Article 162.

Article 71

Market exclusivity

1. Where an orphan marketing authorisation is granted and without prejudice to intellectual property law, the Union and the Member States shall not grant a marketing authorisation or extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product for the duration of market exclusivity set out in paragraph 2.

2. The duration of market exclusivity shall be as follows:

   (a) nine years for orphan medicinal products other than those referred to in points (b) and (c);

   (b) ten years for orphan medicinal products addressing a high unmet medical need as referred to in Article 70;

   (c) five years for orphan medicinal products which have been authorised in accordance with Article 13 of [revised Directive 2001/83/EC].

3. Where a marketing authorisation holder holds more than one orphan marketing authorisations for the same active substance, those authorisations shall not benefit from separate market exclusivity periods. The duration of the market exclusivity shall start from the date when the first orphan marketing authorisation was granted in the Union.

4. By way of derogation from paragraph 1, and without prejudice to intellectual property law, the marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:

   (a) the marketing authorisation holder for the original orphan medicinal product has given consent to the second applicant, or

   (b) the marketing authorisation holder for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or

   (c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

5. The submission, validation and assessment of the application for the marketing authorisation and granting the marketing authorisation for a generic or biosimilar product

to the reference medicinal product for which market exclusivity has expired, shall not be prevented by the market exclusivity of a similar product to the reference medicinal product.

6. The market exclusivity of the orphan medicinal product shall not prevent the submission, validation and assessment of an application for a marketing authorisation for a similar medicinal product, including generics and biosimilars, where the remainder of the duration of the market exclusivity is less than two years.

7. Where the Agency adopts scientific guidelines for the application of paragraphs 1 and 4, it shall consult the Commission.

Article 72

Prolongation of market exclusivity

1. The periods of market exclusivity referred to in Article 71, paragraph 2, points (a) and (b), shall be prolonged by 12 months, where the orphan marketing authorisation holder can demonstrate that the conditions referred to in Article 81(2), point (a), and Article 82(1) [of revised Directive 2001/83/EC] are fulfilled.

   The procedures set out in Articles 82(2) to (5) [of revised Directive 2001/83/EC] shall accordingly apply to the prolongation of market exclusivity.

2. The period of market exclusivity shall be prolonged by an additional 12 months for orphan medicinal products referred to in Article 71(2), points (a) and (b), if at least two years before the end of the exclusivity period, the orphan marketing authorisation holder obtains a marketing authorisation for one or more new therapeutic indications for a different orphan condition.

   Such a prolongation may be granted twice, if the new therapeutic indications are each time for different orphan conditions.

3. The orphan medicinal products which benefit from the prolongation of market exclusivity referred to in the paragraph 2 shall not benefit from the additional period of data protection referred to in Article 81(2), point (d), of [revised Directive 2001/83/EC].

4. Article 71(3) equally applies to the prolongations of market exclusivity referred to in paragraphs 1 and 2.

Article 73

Union financial contribution related to orphan medicinal products

The working arrangements referred to in Article 8 of [new fee Regulation][37] shall set out total or partial reductions for the applicable fees and charges payable to the European Medicines Agency as laid down in [new fee Regulation]. Such reductions shall be covered by the Union contribution provided for in Article 154(3), point (a) of this Regulation.

[37] Regulation [XXX] of the European Parliament and of the Council on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council [OJ L X, XX.XX.XXXX, p. X].

CHAPTER VII
PAEDIATRIC MEDICINAL PRODUCTS

Article 74

Paediatric investigation plan

1. A paediatric investigation plan shall specify the timing and all the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned. In addition, it shall describe any measures to adapt the pharmaceutical form, the strength, the route of administration and the eventual administration device of the medicinal product so as to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population.

2. By derogation from paragraph 1, in the following cases an applicant may submit only an initial paediatric investigation plan as referred to in the second subparagraph:

   (a) when the active substance concerned is not yet authorised in any medicinal product in the EU and is intended to treat a novel paediatric condition;

   (b) following the acceptance by the Agency of a justified request from an applicant in accordance with paragraph 3.

   An initial paediatric investigation plan shall contain only the details and the timing of the measures proposed to assess the quality, safety and efficacy of the medicinal product in all subsets of the paediatric population that may be concerned, that are known at the moment of the submission of the request for agreement mentioned in Article 76(1).

   This initial paediatric investigation plan shall also provide a precise timing of when updated versions of the paediatric investigation plan are to be submitted and when a final paediatric investigation plan complying with all the particulars described in paragraph 1, is expected to be submitted to the Agency.

3. When it is not possible, on the basis of scientifically justified reasons, to have a complete paediatric development plan in accordance with the timing given in Article 76(1) an applicant may submit a justified request to the Agency to utilise the procedure mentioned in paragraph 2. The Agency has 20 days to accept or refuse the request and shall immediately inform the applicant and state the reasons for refusal.

4. On the basis of the experience acquired as a result of the operation of this Article or of scientific knowledge, the Commission is empowered to adopt delegated acts in accordance with Article 175 to amend the grounds for granting the possibility to utilise the adapted procedure foreseen in paragraph 2.

Article 75

Waivers

1. In accordance with the procedure set out in Article 78, the Agency may decide that the production of the information referred to in, Article 6(5), point (a), of [revised Directive 2001/83], shall be waived for products or for classes of medicinal products, if there is evidence showing any of the following:

   (a) that the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population;

(b) that the disease or condition for which the specific medicinal product or class is intended occurs only in adult populations, unless when the product is directed at a molecular target that on the basis of existing scientific data, is responsible for a different disease or condition in the same therapeutic area in children than the one for which the specific medicinal product or class of medicinal products is intended for in the adult population;

(c) that the specific medicinal product is likely to not represent a significant therapeutic benefit over existing treatments for paediatric patients.

2. The waiver provided for in paragraph 1 may be issued with reference either to one or more specified subsets of the paediatric population, or to one or more specified therapeutic indications, or to a combination of both.

3. On the basis of the experience acquired as a result of the operation of this Article or of scientific knowledge the Commission is empowered to adopt delegated acts in accordance with Article 175 to amend the grounds for granting a waiver detailed in paragraph 1.

Article 76

Validation of a paediatric investigation plan or of a waiver

1. A paediatric investigation plan or an application for waiver shall be submitted to the Agency with a request for agreement, except in duly justified cases, before the initiation of safety and efficacy clinical studies so as to ensure that a decision on use in the paediatric population of the medicinal product concerned can be given at the time of the marketing authorisation or other application concerned.

2. Within 30 days following receipt of the request referred to in paragraph 1, the Agency shall verify the validity of the request and communicate the result to the applicant.

3. Whenever appropriate, the Agency may ask the applicant to submit additional particulars and documents, in which case the time-limit of 30 days shall be suspended until the supplementary information requested has been provided.

4. In consultation with the Commission and with interested parties, the Agency shall draw up and publish guidelines for the practical application of this Article.

Article 77

Agreement on a paediatric investigation plan

1. After the validation of the proposed paediatric investigation plan referred to in Article 74(1).which is valid in accordance with the provisions of Article 76(2), the Agency shall adopt within 90 days a decision as to whether or not the proposed studies will ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof, and as to whether or not the expected therapeutic benefits, where appropriate also over existing treatments, justify the studies proposed. When adopting its decision, the Agency shall consider whether or not the measures proposed to adapt the pharmaceutical form, the strength, the route of administration and the eventual administration device of the medicinal product for use in different subsets of the paediatric population are appropriate.

2. After the validation of the proposed initial paediatric investigation plan prepared in accordance with the adapted procedure referred to in Article 74(2) first subparagraph, which is valid in accordance with the provisions of Article 76(2), the Agency shall adopt a

decision within 70 days as to whether or not the paediatric investigation plan is expected to ensure the generation of the necessary data determining the conditions in which the medicinal product may be used to treat the paediatric population or subsets thereof, and as to whether or not the expected therapeutic benefits, where appropriate also over existing treatments, justify the studies envisaged.

3. After receiving an updated version of the paediatric investigation plan referred to in Article 74(2), third subparagraph, the Agency shall review it within 30 days.

   After the timeframe laid down in the first subparagraph, without any request from the Agency in accordance with paragraph 5, the updated version of the paediatric investigation plan shall be considered as agreed.

4. When the final paediatric investigation plan referred to in Article 74(2), third subparagraph, is received, the Agency shall adopt within 60 days a decision on the paediatric investigation plan considering all the updated reviews eventually conducted and of the initial decision in accordance with paragraphs 2 and 3.

5. Within time periods referred to in paragraphs 1, 2, 3 or 4 the Agency may request the applicant to propose modifications to the plan or ask for additional information, in which case the time-limits referred to in paragraphs 1, 2, 3 and 4 shall be extended for a maximum of the same number of days. These time-limits shall be suspended until the supplementary information requested has been provided.

6. The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency.

Article 78

Granting of a waiver

1. An applicant may, on the grounds set out in Article 75(1), apply to the Agency for a product-specific waiver.

2. Following the receipt of a valid application in accordance with the provisions of Article 76(2), the Agency shall within 90 days adopt a decision as to whether or not a product-specific waiver shall be granted.

   Whenever appropriate, the Agency may request the applicant to supplement the particulars and documents submitted. Where the Agency avails itself of this option, the 90-day time-limit shall be suspended until such time as the supplementary information requested has been provided.

3. When appropriate, the Agency may of its own motion adopt decisions, on the basis of the grounds set out in Article 75(1), to the effect that a class or a product-specific waiver, as referred to in Article 75(2), should be granted.

4. The Agency may, at any time adopt a decision reviewing an already granted waiver.

5. If a particular product-specific or class waiver is revoked, the requirement set out in Article 6(5) of [revised Directive 2001/83/EC] shall not apply for 36 months from the date of its removal from the list of waivers.

6. The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency.

7. In consultation with the Commission and with interested parties, the Agency shall draw up and publish guidelines for the practical application of this Article.

Article 79

List of waivers

The Agency shall maintain a list of all waivers granted. The list shall be updated regularly and made available to the public.

Article 80

Waivers granted following a negative decision on a paediatric investigation plan

If, having considered a paediatric investigation plan, the Agency concludes that Article 75(1), points (a), (b) or (c), applies to the medicinal product concerned, it shall adopt negative a decision under Article 77, paragraphs 1, 2 or 4.

In such cases, the Agency shall adopt a decision in favour of a waiver under Article 78(3). The two decisions shall be adopted at the same time by the Agency.

The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency.

Article 81

Deferrals

1. At the same time as the application for a paediatric investigation plan is submitted under Article 76(1) or during the assessment for a paediatric investigation plan, the applicant may also make a request for deferral of the initiation or completion of some or all of the measures set out in that plan. Such deferral shall be justified on scientific and technical grounds or on grounds related to public health.

   In any event, a deferral shall be granted when it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population or when studies in the paediatric population will take longer to conduct than studies in adults.

2. The Agency shall adopt a decision on the request referred to in paragraph 1 and inform the applicant thereof. The Agency shall adopt such decision at the same time as the adoption of the positive decision under Article 77, paragraphs 1 or 2.

   A decision in favour of a deferral shall specify the time-limits for initiating or completing the measures concerned.

3. The length of the deferral shall be specified in a decision of the Agency and shall not exceed five years.

4. On the basis of the experience acquired as a result of the operation of this Article, the Commission is empowered to adopt delegated acts in accordance with Article 175 to amend the grounds for granting a deferral referred to in paragraph 1.

Article 82

Prolongation of deferrals

1. In duly justified cases, a request for a prolongation of the deferral, may be submitted, at least 6 months before the expiry of the deferral period. A prolongation of the derogation shall not exceed the duration of the deferral period given under Article 81(3).

   The Agency shall decide on the prolongation within 60 days.

2. Whenever appropriate, the Agency may ask the applicant to submit additional particulars and documents, in which case the time-limit of 60 days shall be suspended until the supplementary information requested has been provided.

3. The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency.

Article 83

Waivers during a public health emergency

1. The decision by the Agency referred to in Article 6(5), point (e) of [revised Directive 2001/83/EC] shall concern only medicinal products intended for the treatment, prevention or medical diagnosis of a serious or life-threatening disease or condition which are directly related to the public health emergency.

2. The decision mentioned under paragraph 1 shall include the grounds for providing such derogation and its duration.

3. At the latest at the date of expiry of the derogation referred to in paragraph 2, the applicant shall submit to the Agency a paediatric investigation plan or an application for a waiver with a request for agreement in accordance with the provisions of Article 76(1).

Article 84

Modification of a paediatric investigation plan

1. If, following the decision agreeing the paediatric investigation plan, the applicant encounters such difficulties with its implementation as to render the plan unworkable or no longer appropriate, the applicant may propose changes or request the Agency to issue a deferral in accordance with Article 81 or a waiver in accordance with Article 75. The Agency shall adopt within 90 days a decision on the basis of the procedure laid down in Article 87. When appropriate, the Agency may request the applicant to supplement the particulars and documents submitted. Where the Agency avails itself of this option, the time-limit shall be suspended until such time as the supplementary information requested has been provided.

2. If, following the decision agreeing the paediatric investigation plan referred to in Article 77, paragraphs 1, 2 and 4, or on the basis of the updated paediatric investigation plan received in accordance with Article 77(3), the Agency, on the base of new scientific information available, considers that the agreed plan or any of its elements are no longer appropriate, it shall request the applicant to propose changes to the paediatric investigation plan.

   The applicant shall submit the changes requested within 60 days.

   Within 30 days, the Agency shall review these changes and adopt a decision on their refusal or acceptance.

3. Within the time period referred to in paragraph 2, third subparagraph, the Agency may request the applicant for additional modifications to the submitted changes or to submit additional information, in those cases the time-limits referred to in paragraph 2, third subparagraph, shall be extended by another 30 days. This time-limit shall be suspended until the supplementary information requested or the additional modifications have been provided.

4. The procedure laid down in Article 87 shall apply for the adoption of decisions by the Agency.

Article 85

Detailed arrangements for applications in relation to paediatric investigation plans, waivers and deferrals

1. In consultation with the Member States, the Commission and interested parties, the Agency shall draw up the detailed arrangements concerning the format and content which applications for agreement or modification of a paediatric investigation plan, and requests for waivers or deferrals are to follow in order to be considered valid and concerning the operation of the compliance check referred to in Articles 48, 49(2), 86 and 90(2) of [revised Directive 2001/83/EC].

2. The detailed arrangement concerning the format and content of applications for agreement of a paediatric investigation plan mentioned in paragraph 1 shall:

   (a) specify which information should be included in an application for agreement or modification of a paediatric investigation plan or requests for a waiver in the cases referred to in Article 75(1);

   (b) be adapted to take into account the specificities of:

      (i) adapted procedure for paediatric investigation plans as referred to in Article 74(2);

      (ii) products intended to be developed only for use in children;

      (iii) products intended to be submitted under the procedure referred to in Article 92.

Article 86

Compliance with the paediatric investigation plan

Where the application is submitted in accordance with the procedures set out in in this Regulation, the Committee for Medicinal Products for Human Use shall verify whether an application for marketing authorisation or variation complies with the requirements laid down in Article 6(5) of [revised Directive 2001/83/EC].

Article 87

Procedure for adopting a decision in relation to paediatric investigation plans, a waiver or a deferral

1. Decisions referred to in Articles 77, 78, 80, 81, 82 and 84 adopted by the Agency shall be supported by scientific conclusions which shall be annexed to the decision.

2. Where the Agency considers it necessary, it may consult the Committee for Medicinal Products for Human Use or the appropriate working parties when preparing the above mentioned scientific conclusions. The outcome of such consultations shall be annexed to the decision.

3. Decisions of the Agency shall be made public after deletion of any information of a commercially confidential nature.

Article 88

Discontinuation of a paediatric investigation plan

Where a paediatric investigation plan, agreed in accordance with the provisions of Article 77, paragraphs 1, 2 and 4, is discontinued, the applicant shall notify the Agency of its intention to discontinue the conduct of the paediatric investigation plan and provide the reasons for such discontinuation no less than six months before the discontinuation.

The Agency shall publish this information.

Article 89

Scientific advice for paediatric developments

Any legal or natural person developing a medicinal product intended for paediatric use or intended for in utero treatment may, prior to the submission of a paediatric investigation plan and during its implementation, request advice from the Agency on the design and conduct of the various tests and studies necessary to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population in accordance with Article 138(1), point (za).

The Agency shall provide advice under this Article free of charge.

Article 90

Data deriving from a paediatric investigation plan

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

   (a) the results of all clinical studies conducted in compliance with an agreed paediatric investigation plan as referred to in Articles 6(5), point (a), of [revised Directive 2001/83/EC] shall be included in the summary of product characteristics and, if appropriate, in the package leaflet; or

   (b) any agreed waiver as referred to in Articles 6(5), points (b) and (c) of [revised Directive 2001/83/EC], shall be recorded in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.

2. If the application complies with all the measures contained in the agreed completed paediatric investigation plan and if the summary of product characteristics reflects the results of studies conducted in compliance with that agreed paediatric investigation plan, the Commission shall include within the marketing authorisation a statement indicating compliance of the application with the agreed completed paediatric investigation plan.

Article 91

Variation of marketing authorisations on the basis of paediatric studies

1. Any clinical study which involves the use in the paediatric population of a medicinal product covered by a marketing authorisation and is sponsored by the marketing authorisation holder, whether or not it is conducted in compliance with an agreed paediatric investigation plan, shall be submitted to the Agency or to the Member States which have previously authorised the medicinal product concerned within six months of completion of the studies concerned.

2. Paragraph 1 shall apply independent of whether or not the marketing authorisation holder intends to apply for a marketing authorisation of a paediatric indication.

3. When products are authorised in accordance with the provisions of this Regulation, the Commission may update the summary of product characteristics and package leaflet, and may vary the marketing authorisation accordingly.

Article 92

Paediatric use marketing authorisation

1. An application for a paediatric use marketing authorisation shall be submitted in accordance with Articles 5 and 6 and shall be accompanied by the particulars and documents necessary to establish quality, safety and efficacy in the paediatric population, including any specific data needed to support an appropriate formulation, pharmaceutical form, strength, route of administration and eventual administration device for the product, in accordance with an agreed paediatric investigation plan. The application shall also include the decision of the Agency agreeing the paediatric investigation plan concerned.
2. Where a medicinal product is or has been authorised in a Member State or in the Union, data contained in the dossier on that product may, where appropriate, be referred to, in accordance with Article 29 or Article 9 of [revised Directive 2001/83/EC], in an application for a paediatric use marketing authorisation.
3. The medicinal product in respect of which a paediatric use marketing authorisation is granted may retain the name of any medicinal product which contains the same active substance and in respect of which the same marketing authorisation holder has been granted authorisation for use in adults.
4. Submission of an application for a paediatric use marketing authorisation shall in no way preclude the right to apply for a marketing authorisation for other therapeutic indications.

Article 93

Rewards for products authorised under the paediatric use marketing authorisation procedure

Where a paediatric use marketing authorisation referred to in Article 92 is granted and includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the product shall benefit from independent data and marketing protection periods referred to in Articles 80 and 81 of [revised Directive 2001/83/EC].

Article 94

Paediatric clinical trials

1. The EU database created by Article 81 of Regulation (EU) No 536/2014 shall include clinical trials carried out in third countries which are:
   (a) contained in an agreed paediatric investigation plan;
   (b) submitted following the provisions of Article 91.
2. For the clinical trials mentioned in paragraph 1 which are conducted in third countries, the description of the following elements shall be entered into the EU database prior to the start of the trial by the clinical trial sponsor, the addressee of the Agency's decision on a paediatric investigation plan referred to in Article 77, or by the marketing authorisation holder as appropriate:
   (a) the clinical trial protocol;
   (b) the investigational medicinal products used;

(c) the therapeutic indications covered;

(d) details of the trial population.

Irrespective of the outcome of a clinical trial within 6 months from the end of the trial the clinical trial sponsor, the addressee of the Agency's decision on a paediatric investigation plan or the marketing authorisation holder as appropriate, shall submit to the EU database a summary of the results of the trial shall be uploaded in the database.

If for justified scientific reasons it is not possible to submit the summary of the result of the trial within 6 months it shall be submitted to the EU database at the latest within twelve months after the trial has ended. The justification for the delay needs also to be submitted in the EU database.

3. In consultation with the Commission, Member States and interested parties, the Agency shall draw up guidance on the nature of the information referred to in paragraph 2.

4. On the basis of the experience acquired as a result of the operation of this Article, the Commission may adopt implementing acts in accordance with the examination procedure referred to in Article 173(2) to amend the details concerning clinical trials conducted in third countries to be submitted to the EU database and referred to in paragraph 2.

Article 95

European network

1. The Agency shall develop a European network of patient representatives, academics, medicines developers, investigators and centres with expertise in the performance of studies in the paediatric population.

2. The objectives of the European network shall be, inter alia, to discuss priorities in the clinical development of medicines for children, in particular in areas of unmet medical need, to coordinate studies relating to paediatric medicinal products, to build up the necessary scientific and administrative competences at European level, and to avoid unnecessary duplication of studies and testing in the paediatric population.

Article 96

Incentives for research in medicinal products for children

Paediatric medicinal products shall be eligible for incentives made available by the Union and by the Member States to support research into, and the development and availability of, paediatric medicinal products.

Article 97

Fees and Union contribution for paediatric activities

1. Where an application for a paediatric use marketing authorisation is submitted in accordance with the procedure laid down in Article 92, the amount of the reduced fees for the examination of the application and the maintenance of the marketing authorisation shall be fixed in accordance with Article 6 of [new fee Regulation[38]].

[38] Regulation [XXX] of the European Parliament and of the Council on fees and charges payable to the European Medicines Agency, amending Regulation (EU) 2017/745 of the European Parliament and of the Council and

2. Assessments of the following by the Agency shall be free of charge:

(a) applications for waivers;

(b) applications for deferrals;

(c) applications for paediatric investigation plans;

(d) compliance with the agreed paediatric investigation plan.

3. The Union contribution provided for in Article 154 shall cover the work of the Agency, including the assessment of paediatric investigation plans, scientific advice and any fee waivers provided for in this Chapter, and shall support the Agency's activities under Articles 94 and 95.

Article 98

Yearly reporting

At least on an annual basis, the Agency shall make public:

(a) a list of the companies and of the products that have benefited from any of the rewards and incentives in this Regulation;

(b) the companies that have failed to comply with any of the obligations in this Regulation;

(c) the number of paediatric investigation plans agreed in accordance with Article 74;

(d) the number of waivers agreed, providing also a summary of their reasons;

(e) a list of deferrals agreed;

(f) the number of paediatric investigation plans completed;

(g) the renewals of the deferrals beyond five years and the detailed reasons provided as mentioned in Article 82;

(h) the scientific advice provided for the development of medicinal products addressed to children.

CHAPTER VIII
PHARMACOVIGILANCE

Article 99

Pharmacovigilance

1. The obligations of marketing authorisation holders laid down in Articles 99 and 100(1) of [revised Directive 2001/83/EC] shall apply to marketing authorisation holders for medicinal products for human use authorised in accordance with this Regulation.

2. The Agency may impose an obligation on a holder of a centralised marketing authorisation to operate a risk management system, as referred to in Article 99(4), point (c) of [revised Directive 2001/83/EC], if there are concerns about the risks affecting the benefit-risk balance of an authorised medicinal product. In that context, the Agency shall also oblige

---

repealing Council Regulation (EC) No 297/95 and Regulation (EU) 658/2014 of the European Parliament and of the Council [OJ L X, XX.XX.XXXX, p. X].

the marketing authorisation holder to submit a risk management plan for the risk-management system that they intend to introduce for the medicinal product concerned.

The obligation referred to in paragraph 2 shall be duly justified, notified in writing, and shall include the timeframe for submission of the risk-management plan.

3. The Agency shall provide the marketing authorisation holder with an opportunity to submit written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.

On the basis of the written observations submitted by the marketing authorisation holder, the Agency shall review its opinion.

4. Where the opinion of the Agency confirms the obligation and unless the Commission returns the opinion to the Agency for further consideration, the marketing authorisation shall be varied accordingly by the Commission in accordance with the procedure set out in Article 13, to:

(a) include the obligation as a condition of the marketing authorisation and the risk management system shall be updated accordingly.

(b) include the measures to be taken as part of the risk management system as conditions of the marketing authorisation referred to in Article 12(4), point (e).

Article 100

Safety announcements

The obligations of marketing authorisation holders laid down in Article 104(1) of [revised Directive 2001/83/EC], and the obligations of the Member States, the Agency and the Commission laid down in paragraphs 2, 3 and 4 of that Article shall apply to the safety announcements referred to in Article 138(1), point (f), of this Regulation concerning medicinal products for human use authorised in accordance with this Regulation.

Article 101

Eudravigilance database

1. The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a database and data processing network (‘Eudravigilance database’) to collate pharmacovigilance information regarding medicinal products authorised in the Union and to allow competent authorities to access that information simultaneously and to share it.

In justified cases, the Eudravigilance database may include pharmacovigilance information with regard to medicinal products used under compassionate use referred to in Article 26 or early access schemes.

The Eudravigilance database shall contain information on suspected adverse reactions in human beings arising from use of the medicinal product within the terms of the marketing authorisation as well as from uses outside the terms of the marketing authorisation, and on those occurring in the course of post-authorisation studies with the medicinal product or associated with occupational exposure.

2. The Agency shall, in collaboration with the Member States and the Commission, draw up the functional specifications for the Eudravigilance database, together with a timeframe for their implementation.

The Agency shall prepare an annual report on the Eudravigilance database and send it to the European Parliament, the Council and the Commission.

Any substantial change to the Eudravigilance database and the functional specifications shall take into account the recommendations of the Pharmacovigilance Risk Assessment Committee.

The Eudravigilance database shall be fully accessible to the competent authorities of the Member States and to the Agency and the Commission. It shall also be accessible to marketing authorisation holders to the extent necessary for them to comply with their pharmacovigilance obligations.

The Agency shall ensure that healthcare professionals and the public have appropriate levels of access to the Eudravigilance database, and that personal data is protected. The Agency shall work together with all stakeholders, including research institutions, healthcare professionals, and patient and consumer organisations, in order to define the 'appropriate level of access' for healthcare professionals and the public to the Eudravigilance database.

The data held on the Eudravigilance database shall be made publicly available in an aggregated format together with an explanation of how to interpret the data.

3. The Agency shall, in collaboration either with the marketing authorisation holder or with the Member State that submitted an individual suspected adverse reaction report to the Eudravigilance database, be responsible for operating procedures that ensure the quality and integrity of the information collected in the Eudravigilance database.

4. Individual suspected adverse reaction reports and follow-ups submitted to the Eudravigilance database by marketing authorisation holders shall be transmitted electronically upon receipt to the competent authority of the Member State where the reaction occurred.

Article 102

Forms for reporting suspected adverse reactions

The Agency shall, in collaboration with the Member States, develop standard web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and patients in accordance with the provisions referred to in Article 106 of [revised Directive 2001/83/EC].

Article 103

Periodic safety update reports repository

The Agency shall, in collaboration with the competent authorities of the Member States and the Commission, set up and maintain a repository for periodic safety update reports ('repository') and the corresponding assessment reports regarding medicinal products authorised in the Union so that they are fully and permanently accessible to the Commission, the competent authorities of the Member States, the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group referred to in Article 37 of [revised Directive 2001/83/EC] ('coordination group').

The Agency shall, in collaboration with the competent authorities of the Member States and the Commission, and after consultation with the Pharmacovigilance Risk Assessment Committee, draw up the functional specifications for the repository.

Any substantial change to the repository and the functional specifications shall always take into account the recommendations of the Pharmacovigilance Risk Assessment Committee.

Article 104

European medicines web-portal and register of studies for environmental risk assessment

1. The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a European medicines web-portal for the dissemination of information on medicinal products authorised or to be authorised in the Union. By means of that portal, the Agency shall make public the following:

   (a) the names of members of the Committees referred to in Article 142, points (d) and (e), and the members of the coordination group, together with their professional qualifications and with the declarations referred to in Article 147(2);

   (b) agendas and minutes from each meeting of the Committees referred to in Article 142, points (d) and (e), and of the coordination group as regards pharmacovigilance activities;

   (c) a summary of the risk management plans for medicinal products authorised in accordance with this Regulation;

   (d) a list of the locations in the Union where pharmacovigilance system master files are kept and contact information for pharmacovigilance enquiries, for all medicinal products authorised in the Union;

   (e) information about how to report to competent authorities of the Member States suspected adverse reactions to medicinal products and the standard structured forms referred to in Article 102 for their web-based reporting by patients and healthcare professionals, including links to national websites;

   (f) Union reference dates and frequency of submission of periodic safety update reports established in accordance with Article 108 of [revised Directive 2001/83/EC];

   (g) protocols and public abstracts of results of the post-authorisation safety studies referred to in Articles 108 and 120 of [revised Directive 2001/83/EC];

   (h) the initiation of the procedure provided for in Article 41(2), and Articles 114, 115 and 116 of [revised Directive 2001/83/EC], the active substances or medicinal products concerned and the issue being addressed, any public hearings pursuant to that procedure and information on how to submit information and to participate in public hearings;

   (i) conclusions of assessments, recommendations, opinions, approvals and decisions taken by the Agency and its Committees under this Regulation and [revised Directive 2001/83/EC], unless it is required that this information is made public by the Agency by other means;

   (j) conclusions of assessments, recommendations, opinions, approvals and decisions taken by the coordination group, the competent authorities of the Member States and the Commission in the framework of the procedures set out in Articles 16, 106, 107 and 108 of this Regulation and of Chapter IX, Sections 3 and 7 of [revised Directive 2001/83/EC].

   The summaries referred to in point (c) shall include a description of any additional risk minimisation measures.

2. In the development and review of the web portal, the Agency shall consult relevant stakeholders, including patient and consumer groups, healthcare professionals and industry representatives.

3. The Agency shall, in collaboration with the Member States and the Commission, set up and maintain a register of environmental risk assessment studies conducted for the purpose of supporting an environmental risk assessment for medicinal products authorised in the Union, unless such information is made public in the Union by different means.

   Information in such register shall be publicly available, unless restrictions are necessary to protect commercially confidential information. For the purpose of setting up such register, the Agency may request marketing authorisation holders and competent authorities to submit results of any such study already completed for products authorised in the Union within [*OP please add the date = 24 months after the date of application of this Regulation*].

Article 105

Literature monitoring

1. The Agency shall monitor selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances. It shall publish the list of active substances being monitored and the medical literature subject to this monitoring.

2. The Agency shall enter into the Eudravigilance database relevant information from the selected medical literature.

3. The Agency shall, in consultation with the Commission, Member States and interested parties, draw up a detailed guide regarding the monitoring of medical literature and the entry of relevant information into the Eudravigilance database.

Article 106

Monitoring of safety of medicinal products

1. The obligations of marketing authorisation holders and of Member States laid down in Article 105 and Article 106 of [revised Directive 2001/83/EC] shall apply to the recording and reporting of suspected adverse reactions for medicinal products for human use authorised in accordance with this Regulation.

2. The obligations of marketing authorisation holders laid down in Article 107 of [revised Directive 2001/83/EC] and the procedures under Articles 107 and 108 of that Directive shall apply to the submission of periodic safety update reports, the establishment of Union reference dates and changes to the frequency of submission of periodic safety update reports for medicinal products for human use authorised in accordance with this Regulation.

   The provisions applicable to the submission of periodic safety update reports laid down in the of Article 108(2), second subparagraph, of that Directive shall apply to marketing authorisation holders of marketing authorisations which were granted before 2 July 2012 and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation until such time as another frequency or other dates of submission of the reports are laid down in the marketing authorisation or are determined in accordance with Article 108 of that Directive.

3. The assessment of the periodic safety update reports shall be conducted by a rapporteur appointed by the Pharmacovigilance Risk Assessment Committee. The rapporteur shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use or the Reference Member State for the medicinal products concerned.

The rapporteur shall prepare an assessment report within 60 days of receipt of the periodic safety update report and send it to the Agency and to the members of the Pharmacovigilance Risk Assessment Committee. The Agency shall send the report to the marketing authorisation holder.

Within 30 days of receipt of the assessment report, the marketing authorisation holder and the members of the Pharmacovigilance Risk Assessment Committee may submit comments to the Agency and to the rapporteur.

Following the receipt of the comments referred to in the third subparagraph, the rapporteur shall within 15 days update the assessment report taking into account any comments submitted, and forward it to the Pharmacovigilance Risk Assessment Committee. The Pharmacovigilance Risk Assessment Committee shall adopt the assessment report with or without further changes at its next meeting and issue a recommendation. The recommendation shall mention the divergent positions with the grounds on which they are based. The Agency shall include the adopted assessment report and the recommendation in the repository set up under Article 103, and forward both to the marketing authorisation holder.

4. In the case of an assessment report that recommends any action concerning the marketing authorisation, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the report by the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisation concerned, including a timetable for the implementation of the opinion. Where this opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

Where the opinion states that regulatory action concerning the marketing authorisation is necessary, the Commission shall adopt a decision, by means of implementing acts, to vary, suspend or revoke the marketing authorisation in accordance with Article 13. Where the Commission adopts such a decision, it may also adopt a decision addressed to the Member States pursuant to Article 57.

5. In the case of a single assessment of periodic safety update reports concerning more than one marketing authorisation in accordance with Article 110(1) of [revised Directive 2001/83/EC] which includes at least one marketing authorisation granted in accordance with this Regulation, the procedure laid down in Article 107 and Article 109 of that Directive shall apply.

6. The final recommendations, opinions and decisions referred to in paragraphs 3, 4 and 5 shall be made public by means of the European medicines web-portal referred to in Article 104.

Article 107

Agency pharmacovigilance related activities

1. Regarding medicinal products for human use authorised in accordance with this Regulation, the Agency shall, in collaboration with the Member States, take the following measures:

   (a) monitor the outcome of risk minimisation measures contained in risk management plans and of conditions referred to in Article 12, paragraph 4, points (d) to (g), or in Article 20, paragraph 1, points (a) and (b), and in Articles 18(1) and 19;

   (b) assess updates to the risk management system;

   (c) monitor the data in the Eudravigilance database to determine whether there are new risks or whether risks have changed and whether those risks impact on the benefit-risk balance.

2. The Pharmacovigilance Risk Assessment Committee shall perform the initial analysis and prioritisation of signals of new risks or risks that have changed or changes to the benefit-risk balance. Where it considers that follow-up action may be necessary, the assessment of those signals and agreement on any subsequent action concerning the marketing authorisation shall be conducted in a timescale commensurate with the extent and seriousness of the issue. Where appropriate, the assessment of those signals may be included in a pending assessment of a periodic safety update report or a pending procedure in accordance with Articles 95 and 114 of [revised Directive 2001/83/EC] or Article 55 of this Regulation.

3. The Agency and competent authorities of the Member States and the marketing authorisation holder shall inform each other in the event of new risks or risks that have changed or changes to the benefit-risk balance being detected.

Article 108

Non-interventional post-authorisation safety studies

1. For non-interventional post-authorisation safety studies concerning medicinal products for human use authorised in accordance with this Regulation which have been imposed in accordance with Articles 13 and 20, the procedure provided for in Article 117, paragraphs 3 to 7, Articles 118, 119, 120 and 121(1) of [revised Directive 2001/83/EC] shall apply.

2. Where, in accordance with the procedure referred to in paragraph 1, the Pharmacovigilance Risk Assessment Committee issues recommendations for the variation, suspension or revocation of the marketing authorisation, the Committee on Medicinal Products for Human Use shall adopt an opinion taking into account the recommendation, and the Commission shall adopt a decision in accordance with Article 13.

   Where the opinion of the Committee for Medicinal Products for Human Use differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences, together with the recommendation.

Article 109

Exchange of information with other organisations

1. The Agency shall collaborate with the World Health Organization in matters of pharmacovigilance and shall take the necessary steps to submit to it, promptly, appropriate

and adequate information regarding the measures taken in the Union which could have a bearing on public health protection in third countries.

The Agency shall make available promptly all suspected adverse reaction reports occurring in the Union to the World Health Organization.

2. The Agency and the European Monitoring Centre for Drugs and Drug Addiction shall exchange information that they receive on the abuse of medicinal products including information related to illicit drugs.

Article 110

International collaboration

At the request of the Commission, the Agency shall participate in collaboration with the Member States in international harmonisation and standardisation of technical measures in relation to pharmacovigilance.

Article 111

Cooperation with Member States

The Agency and the Member States shall cooperate to continuously develop pharmacovigilance systems capable of achieving high standards of public health protection for all medicinal products, regardless of the routes of marketing authorisation, including the use of collaborative approaches, to maximise use of resources available within the Union.

Article 112

Reports on pharmacovigilance tasks

The Agency shall perform regular independent audits of its pharmacovigilance tasks and report the results to its Management Board on a 2-yearly basis. The results shall be subsequently published.

CHAPTER IX
REGULATORY SANDBOX

Article 113

Regulatory sandbox

1. The Commission may set up a regulatory sandbox pursuant to a specific sandbox plan, based on a recommendation of the Agency and pursuant to the procedure set out in paragraphs 4 to 7, where all the following conditions are met:

   (a) it is not possible to develop the medicinal product or category of products in compliance with the requirements applicable to medicinal products due to scientific or regulatory challenges arising from characteristics or methods related to the product;

   (b) the characteristics or methods referred to in point (a) positively and distinctively contribute to the quality, safety or efficacy of the medicinal product or category of products or provide a major advantage contribution to patient access to treatment.

2. The regulatory sandbox shall set out a regulatory framework, including scientific requirements, for the development and, where appropriate clinical trials and placing on the market of a product referred to in paragraph 1 under the conditions set out in this Chapter.

The regulatory sandbox may allow targeted derogations to this Regulation, [revised Directive 2001/83/EC] or Regulation (EC) 1394/2007 under the conditions set out in Article 114.

A regulatory sandbox shall take effect under direct supervision of the competent authorities of the Member States concerned with a view to ensuring compliance with the requirements of this Regulation and, where relevant, other Union and Member State legislation concerned by the sandbox. Any violation of the conditions set out in the decision referred to in paragraph 6 and the identification of any risks to health and to environment shall be immediately notified to the Commission and to the Agency.

3. The Agency shall monitor the field of emerging medicinal products and may request information and data from marketing authorisation holders, developers, independent experts and researchers, and representatives of healthcare professionals and of patients and may engage with them in preliminary discussions.

4. Where the Agency considers it appropriate to set up a regulatory sandbox for medicinal products which are likely to fall under the scope of this Regulation, it shall provide a recommendation to the Commission. The Agency shall list eligible products or category of products in that recommendation and shall include the sandbox plan referred to in paragraph 1.

   The Agency shall not recommend to set up a regulatory sandbox for a medicinal product that is already advanced in its development programme.

5. The Agency shall be responsible for developing a sandbox plan based on data submitted by developers of eligible products and following appropriate consultations. The plan shall set out clinical, scientific and regulatory justification for a sandbox, including the identification of the requirements of this Regulation, [revised Directive 2001/83/EC] and Regulation (EC) 1394/2007 that cannot be complied with and a proposal for alternative or mitigation measures, where appropriate. The plan shall also include a proposed timeline for the duration of the sandbox. Where appropriate, the Agency shall also propose measures in order to mitigate any possible distortion of market conditions as a consequence of establishing a regulatory.

6. The Commission shall, by means of implementing acts, take a decision on the set up of a regulatory sandbox taking into account the recommendation of the Agency and the sandbox plan pursuant to paragraph 4. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

7. Decisions establishing a regulatory sandbox under paragraph 5 shall be limited in time and shall set out detailed conditions for its implementation. These Decisions shall:

   (a) include the proposed sandbox plan;

   (b) include the duration of the regulatory sandbox and its expiry;

   (c) include as part of the sandbox plan the requirements of this Regulation and of [revised Directive 2001/83/EC] that cannot be complied with and shall include appropriate measures to mitigate potential risks to health and to the environment.

8. The Commission may, by means of implementing acts, suspend or revoke a regulatory sandbox at any time. in any of the following cases:

   (a) the requirements and conditions laid down in paragraphs 6 and 7 are no longer met;

   (b) it is appropriate to protect public health.

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

Where the Agency receives information that one of the cases referred to in the first subparagraph may be fulfilled, it shall inform the Commission accordingly.

9. Where after the Decision to establish the regulatory sandbox in accordance with paragraph 6, risks to health are identified but these risks can be fully mitigated by the adoption of supplementary conditions, the Commission may, after consultation of the Agency, amend its decision by means of implementing acts. The Commission may also prolong the duration of a regulatory sandbox by means of implementing acts. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

10. This Article shall not exclude the setting up of time limited pilot projects to test different ways of implementing the applicable legislation.

Article 114

Products developed under a sandbox

1. When authorising a clinical trial application for products covered by a regulatory sandbox, Member States shall take the sandbox plan referred to in Article 113(1) into consideration.

2. A medicinal product developed as part of a regulatory sandbox may be placed on the market only when authorised in accordance with this Regulation. The initial validity of such authorisation shall not exceed the duration of the regulatory sandbox. The authorisation may be prolonged at the request of the marketing authorisation holder.

3. In duly justified cases, the marketing authorisation of a medicinal product developed under the regulatory sandbox may include derogations from the requirements set out in this Regulation and [revised Directive 2001/83/EC]. Those derogations may entail adapted, enhanced, waived or deferred requirements. Each derogation shall be limited to what is apt and strictly necessary to attain the objectives pursued, duly justified and specified in the conditions to the marketing authorisation.

4. For medicinal products developed as part of a regulatory sandbox for which a marketing authorisation has been granted in accordance with paragraph 2 and where appropriate paragraph 3, the summary of product characteristics and the package leaflet shall indicate that the medicinal product has been developed as part of a regulatory sandbox.

5. Without prejudice to Article 195 of [revised Directive 2001/83/EC], the Commission shall suspend a marketing authorisation granted in accordance with paragraph 2, where the regulatory sandbox has been suspended or revoked in accordance with Article 113(7).

6. The Commission shall immediately vary the marketing authorisation to take account of the mitigation measures taken in accordance with Article 115.

Article 115

General sandbox provisions

1. The regulatory sandboxes shall not affect the supervisory and corrective powers of the competent authorities. In case of identification of risks to public health or safety concerns associated with the use of products covered by a sandbox, competent authorities shall take immediate and adequate temporary measures in order to suspend or restrict their use and inform the Commission in accordance with Article 113(2).

Where such mitigation is not possible or proves to be ineffective, the development and testing process shall be suspended without delay until an effective mitigation takes place.

2. Participants in the regulatory sandbox, in particular the marketing authorisation holder of the medicinal product concerned, shall remain liable under applicable Union and Member States liability legislation for any harm inflicted on third parties as a result from the testing taking place in the sandbox. They shall inform the Agency without undue delay of any information which might entail the amendment of the regulatory sandbox or concerns the quality, safety or efficacy of products developed as part of a regulatory sandbox.

3. The modalities and the conditions of the operation of the regulatory sandboxes, including the eligibility criteria and the procedure for the application, selection, participation and exiting from the sandbox, and the rights and obligations of the participants shall be set out in implementing acts. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

4. The Agency with input from Member States shall submit annual reports to the Commission on the results from the implementation of a regulatory sandbox, including good practices, lessons learnt and recommendations on their setup and, where relevant, on the application of this Regulation and other Union legal acts supervised within the sandbox. These reports shall be made publicly available by the Commission.

5. The Commission shall review the reports and put forward, as appropriate, legislative proposals with a view to update the regulatory framework referred to in Article 113(2) or delegated acts in accordance with Article 28 of [revised Directive 2001/83/EC].

CHAPTER X
AVAILABILITY AND SECURITY OF SUPPLY OF MEDICINAL PRODUCTS

SECTION 1

MONITORING AND MANAGEMENT OF SHORTAGES AND CRITICAL SHORTAGES

Article 116

Marketing authorisation holder notifications

1. The marketing authorisation holder of a medicinal product in possession of a centralised marketing authorisation or a national marketing authorisation ('the marketing authorisation holder') shall notify the competent authority of the Member State where the medicinal product has been placed on the market and, in addition, the Agency for a medicinal product covered by a centralised marketing authorisation (these are referred to in this Chapter as 'the competent authority concerned') of the following:

   (a) its decision to permanently cease the marketing of a medicinal product in that Member State no less than twelve months before the last supply of that medicinal product into the market of a given Member State by the marketing authorisation holder;

   (b) its request to permanently withdraw the marketing authorisation for that medicinal product authorised in that Member State no less than twelve months before the last

supply of that medicinal product into the market of a given Member State by the marketing authorisation holder;

(c) its decision to temporarily suspend the marketing of a medicinal product in that Member State no less than six months before the start of the temporary suspension of supply of that medicinal product into the market of a given Member State by the marketing authorisation holder;

(d) a temporary disruption in supply of a medicinal product in a given Member State, of an expected duration of in excess of two weeks or, based on the demand forecast of the marketing authorisation holder no less than six months before the start of such temporary disruption of supply or, if this is not possible and where duly justified, as soon as they become aware of such temporary disruption, to allow the Member State to monitor any potential or actual shortage in accordance with Article 118(1).

2. For the purposes of the notification made in accordance with paragraph 1, points (a), (b) and (c), the marketing authorisation holder shall provide the information set out in Part I of Annex IV.

For the purpose of notifications made in accordance with the paragraph 1, point (d), the marketing authorisation holder shall provide the information set out in Part III of Annex IV.

The marketing authorisation holder shall immediately notify the competent authority concerned, as appropriate, of any relevant changes to the information provided according to this paragraph.

3. The Commission is empowered to adopt delegated acts, in accordance with Article 175 in order to amend Annex IV as regards the information to be provided in case of a temporary disruption of supply, information to be provided in case of a suspension or cessation of marketing of a medicinal product or withdrawal of the marketing authorisation of a medicinal product, or the content of the shortage prevention plan referred to in Article 117.

Article 117

The shortage prevention plan

1. The marketing authorisation holder as defined in Article 116(1) shall have in place and keep up to date a shortage prevention plan, for any medicinal product placed on the market. To put in place the shortage prevention plan, the marketing authorisation holder shall include the minimum set of information set out in Part V of Annex IV and take into account the guidance drawn up by the Agency according to paragraph 2.

2. The Agency, in collaboration with the working party referred to in Article 121(1), point (c), shall draw up guidance to marketing authorisation holders as defined in Article 116(1) to put in place the shortage prevention plan.

3. Where relevant, the marketing authorisation holder as defined in Article 116(1) shall update the shortage prevention plan to include additional information, based on recommendations of the Executive Steering Group on Shortages and Safety of Medicinal Products (also referred to as the Medicine Shortages Steering Group – 'MSSG', established in Article 3(1) of Regulation (EU) 2022/123, in accordance with Articles 123(4) and 132(1).

Article 118

Shortage monitoring by the competent authority of the Member State or the Agency

1. Based on the reports referred to in Articles 120(1) and 121(1), point (c), information referred to in Articles 119, 120(2) and 121 and the notification made pursuant to Article 116(1), points (a) to (d), the competent authority concerned as referred to in Article 116(1) shall continuously monitor any potential or actual shortage of those medicinal products.

   The Agency shall carry out that monitoring in collaboration with the relevant competent authority of the Member State when those medicinal products are authorised under this Regulation.

2. For the purposes of paragraph 1, the competent authority concerned as defined in Article 116(1) may request any additional information from the marketing authorisation holder as defined in Article 116(1). In particular, it may request the marketing authorisation holder to submit a shortage mitigation plan in accordance with Article 119(2), a risk assessment of impact of suspension, cessation or withdrawal in accordance with Article 119(3), or the shortage prevention plan referred to in Article 117. The competent authority concerned may set a deadline for the submission of the information requested.

Article 119

Obligations on the marketing authorisation holder

1. The marketing authorisation holder as defined in Article 116(1) shall:

   (a) submit the information requested in accordance with Article 118(2) or Article 124(2), point (b) to the competent authority concerned as defined in Article 116(1), without undue delay, using the tools, methods of and criteria for the monitoring and reporting established pursuant to Article 122(4), point (b), by the deadline set by that competent authority;

   (b) provide updates to the information provided in accordance with point (a), where necessary;

   (c) justify any failure to provide any of the requested information;

   (d) where necessary, submit a request to the competent authority concerned as defined in Article 116(1) for an extension of the deadline set by that competent authority in accordance with point (a), and

   (e) indicate whether the information provided in accordance with point (a) contains any commercially confidential information, identify the relevant parts of that information having a commercially confidential nature and explain why that information is of such nature.

2. To prepare the shortage mitigation plan referred to in Article 118(2), the marketing authorisation holder as defined in Article 116(1) shall include the minimum set of information set out in Part IV of Annex IV and take into account the guidance drawn up by the Agency according to Article 122(4), point (c).

3. To prepare a risk assessment of impact of suspension, cessation or withdrawal referred to in Article 118(2), the marketing authorisation holder as defined in Article 116(1) shall include the minimum set of information set out in Part II of Annex IV and take into account the guidance drawn up by the Agency according to Article 122(4), point (c).

4. The marketing authorisation holder as defined in Article 116(1) shall be responsible for providing correct, not misleading, and complete information as requested by the competent authority concerned.

5. The marketing authorisation holder as defined in Article 116(1) shall cooperate with that competent authority and disclose, on their own motion, any relevant information to that authority and update the information as soon as new information becomes available.

Article 120

Obligations on other actors

1. Wholesale distributors and other persons or legal entities that are authorised or entitled to supply medicinal products authorised to be placed on the market of a Member State pursuant to Article 5 of [revised Directive 2001/83/EC] to the public may report a shortage of a given medicinal product marketed in the Member State concerned to the competent authority in that Member State.

2. For the purposes of Article 118(1), where relevant, upon request from the competent authority concerned as defined in Article 116(1), entities including other marketing authorisation holders as defined in Article 116(1), importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public shall provide any information requested in a timely manner.

Article 121

Role of the competent authority of the Member State

1. The competent authority of the Member State shall:

   (a) assess the merits of each confidentiality claim made by the marketing authorisation holder as defined in Article 116(1) in accordance with Article 119(1), point (e), and shall protect information which that competent authority considers to be commercially confidential against unjustified disclosure;

   (b) publish information on actual shortages of medicinal products, in cases in which that competent authority has assessed the shortage, on a publicly available website;

   (c) report to the Agency, through the single point of contact working party referred to in Article 3(6) of Regulation (EU) 2022/123, any shortage of a medicinal product that it identifies as a critical shortage in that Member State to the Agency without undue delay.

2. Following the reporting referred to in paragraph 1, point (c), and to facilitate the monitoring referred to in Articles 118(1), the competent authority of the Member State shall, through the working party referred to in paragraph 1, point (c):

   (a) submit to the Agency the information referred to in Articles 122(1) or 124(2), point (a), using the tools, methods of and criteria for the monitoring and reporting established pursuant to Article 122(4), point (b), by the deadline set by the Agency;

   (b) where necessary, provide updates to the information provided in accordance with point (a) to the Agency;

(c) justify any failure to provide any of the information referred to in point (a) to the Agency;

(d) where necessary, submit a request to the Agency to extend the deadline set by the Agency referred to in point (a);

(e) indicate whether the marketing authorisation holder as defined in Article 116(1) has indicated the existence of any commercially confidential information and provide the marketing authorisation holder's explanation of why that information is of a commercially confidential nature, in accordance with Article 119(1), point (e);

(f) inform the Agency of any actions foreseen or taken by that Member State to mitigate the shortage at national level.

3. Where the competent authority of the Member State has any information in addition to the information to be provided pursuant to this Article, it shall immediately provide such information to the Agency through the working party referred to in paragraph 1, point (c).

4. Following the addition of a medicinal product on the list of critical shortages of medicinal products referred to in Article 123(1), the competent authority of the Member State shall, through the working party referred to in paragraph 1, point (c), provide any information requested pursuant to Article 124(2), point (a), to the Agency.

5. Following any MSSG recommendations provided in accordance with Article 123(4), the competent authority of the Member State shall, through the working party referred to in paragraph 1, point (c):

(a) report to the Agency on any information received from the marketing authorisation holder as defined in Article 116(1) of the medicinal product concerned or from other actors pursuant to Article 120(2);

(b) comply and coordinate with any measures taken by the Commission pursuant to Article 126(1), point (a);

(c) take into account any MSSG recommendations referred to in Article 123(4);

(d) inform the Agency of any actions foreseen or taken by that Member State in accordance with points (b) and (c) and report on any other actions taken to mitigate or resolve the critical shortage in the Member State, as well as the results of these actions.

6. The Member States may request that the MSSG provide further recommendations, referred to in Article 123(4).

Article 122

Role of the Agency concerning shortages

1. For the purposes of Article 118(1), the Agency may request additional information from the competent authority of the Member State, through the working party referred to in Article 121(1), point (c). The Agency may set a deadline for the submission of the information requested.

2. On the basis of Article 118(1), the Agency, in collaboration with the working party referred to in Article 121(1), point (c), shall identify the medicinal products for which the shortage cannot be resolved without EU coordination.

3. The Agency shall inform the MSSG of the shortages of the medicinal products that have been identified pursuant to paragraph 2.

4. For the purposes of fulfilling the tasks referred to in Articles 118(1), 123 and 124, the Agency shall ensure the following, in consultation with the working party referred to in Article 121(1), point (c):

(a) set the criteria to adopt and review the list of critical shortages referred to in Article 123(1);

(b) specify the tools, including the European Shortages Monitoring Platform ('ESMP'), established by Regulation (EU) 2022/123, once the scope is expanded pursuant to paragraph 6, the methods of and criteria for the monitoring and reporting provided for in Articles 119(1), point (a), and 121(2), point (a);

(c) draw up guidance to allow marketing authorisation holders as defined in Article 116(1) to put in place the risk assessment of impact of suspension, cessation or withdrawal and the shortage mitigation plan as referred to in Article 118(2);

(d) specify the methods for the provision of recommendations referred to in Article 123(4);

(e) publish information covered by points (a) to (d) on a dedicated webpage on its web-portal referred to in Article 104.

5. For the duration of the critical shortage and until the MSSG considers it to be resolved, the Agency shall regularly report on the results of the monitoring referred to in Article 124 to the Commission and the MSSG, and in particular, it shall report any event that is likely to lead to a major event, as defined in Article 2 of Regulation (EU) 2022/123. Where a public health emergency is recognised in accordance with Regulation (EU) 2022/2371 or an event is recognised as a major event, in accordance with Regulation (EU) 2022/123, that Regulation applies.

6. For the purposes of implementing this Regulation, the Agency shall expand the scope of the ESMP. The Agency shall ensure that, where relevant, data is interoperable between the ESMP, Member States' IT systems and other relevant IT systems and databases, without duplication of reporting.

Article 123

Role of the MSSG and the list of critical shortages of medicinal products

1. Based on the monitoring referred to in Article 118(1), and following consultation with the Agency and the working party referred to in Article 121(1), point (c), the MSSG shall adopt a list of critical shortages of medicinal products authorised to be placed on the market of a Member State pursuant to Article 5 of [revised Directive 2001/83/EC]and for which co-ordinated Union level action is necessary ('the list of critical shortages of medicinal products').

2. The MSSG shall review the status of the critical shortage whenever necessary and shall update the list when it considers that a medicinal product needs to be added or that the critical shortage has been resolved based on the report pursuant to Article 122(5).

3. In addition, the MSSG shall amend its rules of procedure, and the rules of procedure of the working party referred to in Article 121(1), point (c), in accordance with the roles set out in this Regulation.

4. The MSSG may provide recommendations on measures to resolve or to mitigate the critical shortage, in accordance with the methods referred to in Article 122(4), point (d), to

relevant marketing authorisation holders, the Member States, the Commission, the representatives of healthcare professionals or other entities.

Article 124

Management of the critical shortage

1. Following the addition of a medicinal product to the list of critical shortages pursuant to Article 123, paragraphs 1 and 2, and based on the continuous monitoring carried out in accordance with Article 118(1), the Agency, in coordination with the competent authority of the Member State, shall continuously monitor the critical shortage of that medicinal product.

2. For the purposes of paragraph 1, where that information is not already available to the Agency, the Agency may request relevant information on that critical shortage from:

   (a) the competent authority of the Member State concerned through the working party referred to in Article 121(1), point (c);

   (b) the marketing authorisation holder as defined in Article 116(1);

   (c) the other actors listed in Article 120(2).

   For the purposes of this paragraph, the Agency may set a deadline for the submission of the information requested.

3. The Agency shall establish within its web-portal referred to in Article 104 a publicly available webpage that provides information on actual critical shortages of medicinal products in cases in which the Agency has assessed the shortage and has provided recommendations to healthcare professionals and patients. This webpage shall also provide references to the lists of actual shortages published by the competent authorities of the Member State pursuant to Article 121(1), point (b).

Article 125

Obligations on the marketing authorisation holder in case of a critical shortage

1. Following the addition of a medicinal product to the list of critical shortages of medicinal products in accordance with Article 123, paragraphs 1 and 2, or recommendations provided in accordance with Article 123(4), the marketing authorisation holder as defined in Article 116(1) and subject to those recommendations shall:

   (a) provide any additional information that the Agency may request;

   (b) provide additional relevant information to the Agency;

   (c) take into account the recommendations referred to in Article 123(4);

   (d) comply with any measures taken by the Commission pursuant to Article 126(1), point (a), or actions taken by the Member State pursuant to Article 121(5), point (d);

   (e) inform the Agency of any measures taken pursuant to points (c) and (d) and the report on results of such measures;

   (f) inform the Agency of the end date of the critical shortage.

Article 126

Role of the Commission

1. The Commission shall, where it considers it appropriate and necessary:

   (a) take into account the MSSG recommendations and implement relevant measures;

   (b) inform the MSSG of those measures taken by the Commission.

2. The Commission may request the MSSG to provide recommendations referred to in Article 123(4).

SECTION 2

SECURITY OF SUPPLY

Article 127

Identification and management of critical medicinal products by the competent authority of the Member State

1. The competent authority of the Member State shall identify critical medicinal products in that Member State, using the methodology set out in Article 130(1), point (a).

2. The competent authority of the Member State acting through the working party referred to in Article 121(1), point (c), shall report to the Agency the critical medicinal products in that Member State identified pursuant to the paragraph 1, as well as the information received from the marketing authorisation holder as defined in Article 116(1).

3. For the purposes of the identification of critical medicinal products referred to in paragraph 1, the competent authority of the Member State may request relevant information including the shortage prevention plan referred to in Article 117 from the marketing authorisation holder as defined in Article 116(1).

4. For the purposes of the identification of critical medicinal products referred to in paragraph 1, the competent authority of the Member State may request relevant information from other entities including other marketing authorisation holders, importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public.

5. The competent authority of the Member State shall assess the merits of each confidentiality claim made by the marketing authorisation holder pursuant to Article 128(1), point (e), and shall protect any information that is commercially confidential against unjustified disclosure.

6. For the purposes of the adoption of the Union list of critical medicinal products pursuant to Article 131, each Member State shall, through the competent authority of the Member State concerned:

   (a) submit to the Agency the information referred to in Article 130(2), point (a), using the tools, methods of and criteria for the monitoring and reporting established pursuant to Article 130(1), point (c), by the deadline set by the Agency;

   (b) provide any relevant information to the Agency, including information on measures that have been taken by the Member State to strengthen the supply of that medicinal product;

   (c) provide updates to the information provided in accordance with points (a) and (b) to the Agency where necessary;

(d) justify any failure to provide any of the requested information;

(e) indicate the existence of any commercially confidential information reported as such by the marketing authorisation holder pursuant to Article 128(1), point (e), and provide the marketing authorisation holder's explanation of why that information is of a commercially confidential nature.

Where necessary, the competent authority of the Member State may request an extension of the deadline set by the Agency to comply with the request for information in accordance with point (a) of the first subparagraph.

7. Following the addition of a medicinal product to the Union list of critical medicinal products in accordance with Article 131 or any recommendations provided in accordance with Article 132(1), the Member States shall:

(a) provide any additional information that the Agency may request;

(b) provide additional relevant information to the Agency;

(c) comply and coordinate with any measures taken by the Commission pursuant to Article 134(1), point (a);

(d) take into account any MSSG recommendations referred to in Article 132(1);

(e) inform the Agency of any actions foreseen or taken in accordance with point (c) and (d) by that Member State, as well as the results of these actions.

8. Member States that take an alternative course of action in respect of paragraph 7, points (c) and (d), shall share the reasons for doing so with the Agency in a timely manner.

Article 128

Obligations of the marketing authorisation holder with regard to critical medicinal products

1. For the purposes of Article 127, paragraphs 1 and 3, and Article 131(1), the marketing authorisation holder as defined in Article 116(1) shall:

(a) submit the information requested in accordance with Articles 127(3), 130(2), point (b), and 130(4), point (b), to the competent authority concerned as defined in Article 116(1), without undue delay, using the tools, methods of and criteria for the monitoring and reporting established pursuant to Article 130(1), point (c), by the deadline set by that competent authority concerned;

(b) provide updates to the information provided in accordance with point (a) where necessary;

(c) justify any failure to provide any of the requested information;

(d) where necessary, submit a request to the competent authority concerned as defined in Article 116(1) for an extension of the deadline set by that competent authority in accordance with point (a), and

(e) indicate whether the information provided in accordance with point (a) contain any commercially confidential information, identify the relevant parts of that information having a commercially confidential nature and explain why that information is of such nature.

2. The marketing authorisation as defined in Article 116(1) authorisation shall be responsible for providing correct, not misleading, and complete information as requested by the competent authority concerned as defined in Article 116(1) and shall have the duty to

cooperate and to disclose on their own motion any relevant information without undue delay to that competent authority and to update the information as soon as that information becomes available.

Article 129

Obligations on other actors

For the purposes of Article 127(4) and Article 130(2), point (c), and Article 130(4), point (c), where relevant, upon request from the competent authority concerned as defined in Article 116(1), entities including other marketing authorisation holders as defined in Article 116(1), importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public shall provide any information requested in a timely manner.

Article 130

Role of the Agency

1. The Agency shall, in collaboration with the working party referred to in Article 121(1), point (c), ensure the following:

   (a) develop a common methodology to identify critical medicinal products, including the evaluation of vulnerabilities with respect to the supply chain of those medicines, in consultation, where appropriate, with relevant stakeholders;

   (b) specify the procedures and criteria for establishing and reviewing the Union list of critical medicinal products referred to in Article 131;

   (c) specify the tools, methods of and criteria for the monitoring and reporting provided for in Articles 127(6), point (a), and 128(1), point (a);

   (d) specify the methods for the provision and review of MSSG recommendations referred to in Article 132, paragraphs 1 and 3.

   The Agency shall publish the information referred to in points (b), (c) and (d) on a dedicated webpage on its web-portal.

2. Following the reports and information provided by the Member States and marketing authorisation holders in accordance with Article 127, paragraphs 2 and 6, and Article 128(1), the Agency, may request the relevant information from:

   (a) the competent authority of the Member State concerned;

   (b) the marketing authorisation holder of the medicinal product, including the shortage prevention plan, referred to in Article 117;

   (c) other entities including other marketing authorisation holders, importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public.

   The Agency, in consultation with the working party referred to in Article 121(1), point (c), shall report the information referred to in Article 127, paragraphs 2 and 6, and Article 128(1) to the MSSG.

3. For the purposes of Article 127(6), point (e), and Article 128(1), point (e), the Agency shall assess the merits of each confidentiality claim and protect commercially confidential information against unjustified disclosure.

4. Following the adoption of the Union list of critical medicinal products in accordance with Article 131, the Agency may request additional information from:

   (a) the competent authority of the Member State concerned;

   (b) the marketing authorisation holder as defined in Article 116(1);

   (c) other entities including other marketing authorisation holders, importers and manufacturers of medicinal products or active substances and relevant suppliers of these, wholesale distributors, stakeholder representative associations or other persons or legal entities that are authorised or entitled to supply medicinal products to the public.

5. Following the adoption of the Union list of critical medicinal products in accordance with Article 131, the Agency shall report to the MSSG on any relevant information received from the marketing authorisation holder pursuant to Article 133 and the competent authority of the Member State in accordance with Article 127, paragraphs 7 and 8.

6. The Agency shall make publicly available via the web-portal referred to in Article 104 the MSSG recommendations referred to in Article 132(1).

Article 131

The Union List of Critical Medicinal Products

1. Following the reporting referred to in Article 130, paragraph 2, second subparagraph, and Article 130(5), the MSSG shall consult the working party referred to in Article 121(1), point (c). Based on this consultation, the MSSG shall propose a Union list of critical medicinal products authorised to be placed on the market of a Member State pursuant to Article 5 of [revised Directive 2001/83/EC] and for which coordinated Union level action is necessary ("the Union list of critical medicinal products").

2. The MSSG may propose updates to the Union list of critical medicines to the Commission, where necessary.

3. The Commission, taking into account the proposal of the MSSG, shall adopt and update the Union list of critical medicinal products by means of an implementing act and communicate the adoption of the list and any updates to the Agency and the MSSG. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 173(2).

4. Following the adoption of the Union list of critical medicinal products in accordance with paragraph 3, the Agency shall immediately publish this list and any updates to this list on its web-portal referred to in Article 104.

Article 132

Role of the MSSG

1. Following the adoption of the Union list of critical medicinal products pursuant to Article 131(3), in consultation with the Agency and the working party referred to in Article 121(1), point (c), the MSSG may provide recommendations, in accordance with the methods referred to in Article 130(1), point (d), on appropriate security of supply measures

to marketing authorisation holders as defined in Article 116(1), the Member States, the Commission or other entities. Such measures may include recommendations on diversification of suppliers and inventory management.

2. The MSSG shall amend its rules of procedure, and the rules of procedure of the working party referred to in Article 121(1), point (c), in accordance with the tasks set out in this section.

3. Following the report pursuant to Article 130(5), the MSSG shall review its recommendations in accordance with the methods referred to in Article 130(1), point (d).

4. The MSSG may request the Agency to request further information from the Member States or marketing authorisation holder of the medicinal product as defined in Article 116(1) and included on the Union list of critical medicinal products or other relevant entities referred to in Article 129.

Article 133

Obligations on the marketing authorisation holder after the MSSG recommendations

Following the addition of a medicinal product to the Union list of critical medicinal products in accordance with Article 131(3) or any recommendations provided in accordance with Article 132(1), the marketing authorisation holder as defined in Article 116(1) of a medicinal product on that list or subject to those recommendations shall:

(a) provide any additional information that the Agency may request;

(b) provide additional relevant information to the Agency;

(c) take into account the recommendations referred to in Article 132(1);

(d) comply with any measures taken by the Commission in accordance with Article 134(1), point (a), or by the Member State pursuant to Article 127(7), point (e);

(e) inform the Agency of any measures taken and report on the results of such measures.

Article 134

Role of the Commission

1. The Commission may, where it considers it appropriate and necessary:

   (a) take into account the MSSG recommendations and implement the relevant measures;

   (b) inform the MSSG of those measures taken by the Commission.

   (c) request the MSSG to provide information or an opinion or further recommendations referred to in Article 132(1).

2. The Commission, taking into consideration the information or the opinion, referred to in paragraph 1, or MSSG recommendations, may decide to adopt an implementing act to improve security of supply. The implementing act may impose contingency stock requirements of active pharmaceutical ingredient or finished dosage forms, or other relevant measures required to improve security of supply, on marketing authorisation holders, wholesale distributors or other relevant entities.

3. The implementing act referred to in paragraph 2 shall be adopted in accordance with the examination procedure referred to in Article 173(2).

CHAPTER XI
EUROPEAN MEDICINES AGENCY

SECTION 1

TASKS OF THE AGENCY

Article 135

Establishment

The functioning of the European Medicines Agency established by Regulation (EC) No 726/2004 (the 'Agency') shall continue in accordance with the present Regulation.

The Agency shall be responsible for coordinating the existing scientific resources put at its disposal by Member States for the evaluation, supervision and pharmacovigilance of medicinal products for human use and of veterinary medicinal products.

Article 136

Legal status

1. The Agency shall have legal personality.
2. In each of the Member States, the Agency shall enjoy the most extensive legal capacity accorded to legal persons under their laws. It may, in particular, acquire or dispose of movable and immovable property, and be party to legal proceedings.
3. The Agency shall be represented by an Executive Director.

Article 137

Seat

The seat of the Agency shall be established in Amsterdam, the Netherlands.

Article 138

Objectives and tasks of the Agency

1. The Agency shall provide the Member States and the institutions of the Union with the best possible scientific opinion on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human use, veterinary medicinal products, which is referred to it in accordance with the Union legal acts relating to medicinal products for human use or veterinary medicinal products.

   The Agency, acting particularly through its Committees, shall carry out the following tasks:

   (a) coordinating the scientific evaluation of the quality, safety and efficacy of medicinal products for human use, which are subject to Union marketing authorisation procedures;

   (b) coordinating the scientific evaluation of the quality, safety and efficacy of veterinary medicinal products, which are subject to Union marketing authorisation procedures

in accordance with Regulation (EU) 2019/6 and the performance of other tasks set out in Regulation (EU) 2019/6 and Regulation (EC) 470/2009;

(c) transmitting on request and making publicly available assessment reports, summaries of product characteristics, labels and package leaflets for the medicinal products for human use;

(d) coordinating the monitoring of medicinal products for human use which have been authorised in the Union and providing advice on the measures necessary to ensure the safe and effective use of those products, in particular by coordinating the evaluation and implementation of pharmacovigilance obligations and systems and the monitoring of such implementation;

(e) ensuring the collation and dissemination of information on suspected adverse reactions to medicinal products for human use authorised in the Union by means of databases that are permanently accessible to all Member States;

(f) assisting Member States with the rapid communication of information on pharmacovigilance concerns relating to medicinal products for human use to healthcare professionals and coordinating the safety announcements of the competent authorities of the Member States;

(g) distributing appropriate information on pharmacovigilance concerns relating to medicinal products for human use to the general public, in particular by setting up and maintaining a European medicines web-portal;

(h) coordinating, as regards medicinal products for human use and veterinary medicinal products, the verification of compliance with the principles of good manufacturing practice, good laboratory practice, good clinical practice, good pharmacovigilance practice and, as regards medicinal products for human use, the verification of compliance with pharmacovigilance obligations;

(i) ensuring the secretariat of the Joint Audit Programme referred to in Article 54;

(j) upon request, providing technical and scientific support in order to improve cooperation between the Union, its Member States, international organisations and third countries on scientific and technical issues relating to the evaluation and monitoring of medicinal products for human use and of veterinary medicinal products, in particular in the framework of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and the Veterinary International Conference on Harmonization;

(k) coordinating as referred to in Article 53 a structured cooperation on inspections in third countries between Member States, the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe, the World Health Organization or trusted international authorities, by means of international inspection programmes;

(l) conducting inspections with Member States to verify the compliance with the principles of good manufacturing practice, including issuing GMP certificates and good clinical practice at the request of the Supervisory Authority referred to in Article 50(2) whenever additional capacity is needed to carry out inspection of Union interest including in response of public health emergencies;

(m) recording the status of marketing authorisations for medicinal products for human use granted in accordance with Union marketing authorisation procedures;

(n) creating a database on medicinal products for human use, to be accessible to the general public, and ensuring that it is updated, and managed independently of pharmaceutical companies; the database is to facilitate the search for information already authorised for package leaflets; it is to include a section on medicinal products for human use authorised for the treatment of children; the information provided to the general public is to be worded in an appropriate and comprehensible manner;

(o) assisting the Union and its Member States in the provision of information to health-care professionals and the general public about medicinal products for human use and about veterinary medicinal products evaluated by the Agency;

(p) providing scientific advice to undertakings or, as relevant, not-for-profit entities on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of medicinal products for human use;

(q) supporting, through enhanced scientific and regulatory advice, the development of medicinal products which are of major interest from the point of view of public health, including antimicrobial resistance, and in particular from the viewpoint of therapeutic innovation (priority medicines);

(r) checking that the conditions laid down in Union legal acts on medicinal products for human use and on veterinary medicinal products and in the marketing authorisations are met in the case of parallel distribution of medicinal products for human use and on veterinary medicinal products authorised in accordance with this Regulation or, as applicable, Regulation (EU) 2019/6;

(s) drawing up, at the Commission's request, any other scientific opinion concerning the evaluation of medicinal products for human use and of veterinary medicinal products or the starting materials used in the manufacture of medicinal products for human use;

(t) with a view to the protection of public health, compiling scientific information concerning pathogenic agents which might be used in biological warfare, including the existence of vaccines and other medicinal products for human use and other veterinary medicinal products available to prevent or treat the effects of such agents;

(u) coordinating the supervision of the quality of medicinal products for human use and of veterinary medicinal products placed on the market by requesting testing of compliance with their authorised specifications to the European Directorate for the Quality of Medicines and Healthcare that coordinates with the Official Medicines Control Laboratory or by a laboratory that a Member State has designated for that purpose. The Agency and the European Directorate for the Quality of Medicines and Healthcare shall enter into a written contract for the provision of services to the Agency under this subparagraph;

(v) forwarding annually to the budgetary authority aggregated information on procedures for medicinal products for human use and veterinary medicinal products;

(w) taking decisions as referred to in Article 6(5) of [revised Directive 2001/83/EC];

(x) contributing to the joint reporting with the European Food Safety Authority and European Centre for Disease Prevention and Control on the sales and use of antimicrobials in human and veterinary medicine as well as on the situation as regards antimicrobial resistance in the Union based on contributions received by Member States, taking into account the reporting requirements and periodicity in

Article 57 of Regulation (EU) 2019/6. Such joint reporting shall be carried out at least every three years;

(y) adopting a decision granting, refusing or transferring an orphan designation;

(z) adopting decisions on paediatric investigation plans, waivers and deferrals in relation to medicinal products;

(za) providing regulatory support and scientific advice for the development of orphan and paediatric medicinal products;

(zb) coordinating assessment of and certifying quality master files for medicinal products for human use as well as, where necessary, coordinating inspections of manufacturers applying for or holding a certificate for a quality master file;

(zc) establishing a mechanism of consultation of authorities or bodies active along the life cycle of medicinal products for human use for exchange of information and pooling of knowledge on general issues of scientific or technical nature related to the tasks of the Agency;

(zd) developing coherent scientific assessment methodologies in the fields falling within its mission;

(ze) cooperating with EU decentralised agencies and other scientific authorities and bodies established under Union law, notably the European Chemicals Agency, the European Food Safety Authority, the European Centre for Disease Prevention and Control and the European Environment Agency as regards the scientific assessment of relevant substances, exchange of data and information and development of coherent scientific methodologies, including replacing, reducing or refining animal testing, taking into account the specificities of the assessment of medicinal products;

(zf) coordinating the monitoring and management of critical shortages of medicinal products included in the list referred to in Article 123(1);

(zg) coordinating the identification and management of the Union list of critical medicinal products referred to in Article 131;

(zh) supporting the working party referred to in Article 121(1), point (c), and the MSSG in their tasks in relation to critical shortages and critical medicines;

(zi) providing regulatory support and scientific advice for, and facilitate the development, validation and regulatory uptake of new-approach methodologies that replace the use of animals in testing;

(zj) facilitating joint non-clinical studies between applicants and holders to avoid unnecessary duplication of tests using live animals;

(zk) facilitating data sharing of results from non-clinical studies on live animals;

(zl) drawing up scientific guidelines to facilitate the implementation of the definitions established in this Regulation and in [revised Directive 2001/83], and for the environmental risk assessment of medicinal products for human use, in consultation with the Commission and the Member States.

2. The database provided for in paragraph 1, point (n), shall include all medicinal products for human use authorised in the Union together with the summaries of product characteristics, the package leaflet and the information shown on the labelling. Where relevant, it shall include the electronic links to the dedicated webpages where the marketing authorisation

holders have reported the information pursuant to Article 40(4), point (b), and Article 57 of [revised Directive 2001/83/EC].

For the purposes of the database, the Agency shall set up and maintain a list of all medicinal products for human use authorised in the Union. To this effect:

(a) the Agency shall make public a format for the electronic submission of information on medicinal products for human use;

(b) marketing authorisation holders shall electronically submit to the Agency information on all medicinal products for human use authorised in the Union and shall inform the Agency of any new or varied marketing authorisations granted in the Union, using the format referred to in point (a).

Where appropriate, the database shall also include references to clinical trials currently being carried out or already completed, contained in the clinical trials database provided for in Article 81 of Regulation (EU) No 536/2014.

Article 139

Coherence of scientific opinions with other Union bodies

1. The Agency shall take the necessary and appropriate measures to monitor and identify at an early stage any potential source of divergence between its scientific opinions and the scientific opinions issued by other Union bodies and agencies carrying out similar tasks in relation to issues of common concern.

2. Where the Agency identifies a potential source of divergence, it shall contact the body or agency in question to ensure that all relevant scientific or technical information is shared and in order to identify potentially contentious scientific or technical issues.

3. Where a substantive divergence over scientific or technical issues is identified and the body concerned is a Union Agency or a scientific committee, the Agency and the body concerned shall cooperate to resolve the divergence, and inform the Commission without undue delay.

4. The Commission may ask the Agency to conduct an assessment as regards specifically the use of the substance concerned in medicinal products. The Agency shall make public its assessment stating clearly the reasons for its specific scientific conclusions.

5. To enable coherence between scientific opinions and to avoid duplication of tests, the Agency shall make arrangements with other bodies or agencies established under Union law for cooperation on scientific assessments and methodologies. The Agency shall also make arrangements for the exchange of data and information on relevant substances with the Commission, Member States' authorities and other Union Agencies, in particular for environmental risk assessments, non-clinical studies and maximum residue limits.

   These arrangements shall seek to ensure that exchanges of data and information are made available in electronic formats and shall protect the commercially confidential nature of the information exchanged and be without prejudice to the provisions on regulatory protection.

Article 140

Scientific opinions in the context of international collaboration

1. The Agency may give a scientific opinion, in particular in the context of cooperation with the World Health Organization, for the evaluation of certain medicinal products for human

use intended for markets outside the Union. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. Such application may be submitted and assessed together with a marketing authorisation application or any subsequent variation for the EU. The Agency may, after consulting the World Health Organization, and as appropriate other relevant organisations, draw up a scientific opinion in accordance with Articles 6, 10 and 12. The provisions of Article 13 shall not apply.

2. The Agency shall establish specific procedural rules for the implementation of paragraph 1, as well as for the provision of scientific advice.

Article 141

International regulatory cooperation

1. In so far as is necessary in order to achieve the objectives set out in this Regulation, and without prejudice to the respective competences of the Member States and the institutions of the Union, the Agency may cooperate with the competent authorities of third countries and/or with international organisations.

   To this end, the Agency may, subject to prior approval by the Commission, establish working arrangements with the authorities of third countries and international organisations, with regard to:

   (a) the exchange of information, including non-public information, where relevant jointly with the Commission;

   (b) sharing of scientific resources and expertise, with a view to facilitating collaboration, while maintaining independent assessment in full compliance with the provisions of this Regulation and [revised Directive 2001/83/EC] and under conditions determined beforehand by the Management Board, in agreement with the Commission;

   (c) the participation in certain aspects of the Agency's work, under conditions determined beforehand by the Management Board, in agreement with the Commission.

   These arrangements shall not create legal obligations incumbent on the Union and its Member States.

2. The Agency shall ensure that it is not seen as representing the Union position to an outside audience or as committing the Union to international cooperation.

3. The Commission may, in agreement with the Management Board and the relevant committee, invite representatives of international organisations with an interest in the harmonisation of technical requirements applicable to medicinal products for human use and to veterinary medicinal products to participate as observers in the work of the Agency. The conditions for participation shall be determined in advance by the Commission.

SECTION 2

STRUCTURE AND OPERATION

Article 142

Administrative and management structure

The Agency shall comprise:

(a) a Management Board, which shall exercise the functions set out in Articles 143, 144 and 154.

(b) an Executive Director, who shall exercise the responsibilities set out in Article 145;

(c) a Deputy Executive Director who shall exercise the responsibilities set out in Article 145(7);

(d) the Committee for Medicinal Products for Human Use;

(e) the Pharmacovigilance Risk Assessment Committee;

(f) the Committee for Veterinary Medicinal Products set up pursuant to Article 139(1) of Regulation (EU) 2019/6;

(g) the Herbal Medicinal Products working group set up pursuant to Article 141 of [revised Directive 2001/83/EC];

(h) the Emergency task force set up pursuant to Article 15 of Regulation (EU) 2022/123;

(i) the MSSG set up pursuant to Article 3 of Regulation (EU) 2022/123;

(j) the Medical Device Shortages Steering Group, set up pursuant to Article 21 of Regulation (EU) 2022/123;

(k) the inspection working group;

(l) a Secretariat, which shall provide technical, scientific and administrative support to all bodies of the Agency and ensure appropriate coordination between them, and which shall provide technical and administrative support for the coordination group referred to in Article 37 of [revised Directive 2001/83/EC] and ensure appropriate coordination between it and the Committees. It shall also undertake the work required of the Agency under the procedures for the assessment and preparations of decisions for paediatric investigation plans, waivers, deferrals or orphan designations.

Article 143

Management Board

1. The Management Board shall be composed of one representative from each Member State, two representatives of the Commission and two representatives of the European Parliament, all with voting rights.

   In addition, two representatives of patients' organisations, one representative of doctors' organisations and one representative of veterinarians' organisations, all with voting rights, shall be appointed by the Council in consultation with the European Parliament on the basis of a list drawn up by the Commission which includes appreciably more names than there are posts to be filled. The list drawn up by the Commission shall be forwarded to the European Parliament, together with the relevant background documents. As quickly as possible, and at the latest within three months of notification, the European Parliament may submit its views for consideration to the Council, which shall then appoint these representatives to the Management Board.

   The members of the Management Board shall be appointed in such a way as to guarantee the highest levels of specialist qualifications, a broad spectrum of relevant expertise and the broadest possible geographic spread within the European Union.

2. Members of the Management Board and their alternates shall be appointed on the basis of their knowledge, recognised experience and commitment in the field of medicinal products

for human or veterinary use, taking into account relevant managerial, administrative and budgetary expertise [which are to be used to further the objectives of this Regulation].

All parties represented in the Management Board shall make efforts to limit turnover of their representatives, in order to ensure continuity of the work of the Management Board. All parties shall aim to achieve a balanced representation between men and women on the Management Board.

3. Each Member State and the Commission shall appoint their members of the Management Board as well as an alternate who will replace the member in their absence and vote on their behalf.

4. The term of office for members and their alternates shall be four years. That term shall be extendable.

5. The Management Board shall elect a chairperson and a Deputy chairperson from among its members.

The chairperson and the Deputy chairperson shall be elected by a majority of two-thirds of the members of the Management Board with voting rights.

The Deputy chairperson shall automatically replace the chairperson if they are prevented from attending to their duties.

The term of office of the chairperson and the deputy chairperson shall be four years. The term of office may be renewed once. If however, their membership of the Management Board ends at any time during their term of office, their term of office shall automatically expire on that date.

6. Without prejudice to paragraph 5 and Article 144, points (e) and (g), the Management Board shall take decisions by absolute majority of its members with voting rights.

7. The Management Board shall adopt its rules of procedure.

8. The Management Board may invite the chairpersons of the scientific committees to attend its meetings, but they shall not have the right to vote.

9. The Management Board may invite any person whose opinion may be of interest to attend its meetings as an observer.

10. The Management Board shall approve the annual work programme of the Agency programme and forward it to the European Parliament, the Council, the Commission and the Member States.

11. The Management Board shall adopt the annual report on the Agency's activities and forward it by 15 June at the latest to the European Parliament, the Council, the Commission, the European Economic and Social Committee, the Court of Auditors and the Member States.

Article 144

Tasks of the Management Board

The Management Board shall:

(a) give the general orientations for the Agency's activities;

(b) adopt an opinion on the rules of procedures of the Committee for Medicinal Products for Human Use (Article 148) and the Committee for Veterinary Medicinal Products (Article 139 of Regulation (EU) 2019/6);

(c) adopt procedures for the performance of scientific services regarding medicinal products for human use (Article 152);

(d) appoint the Executive Director, and where relevant extend their term of office or remove them from office, in accordance with Article 145;

(e) adopt yearly the Agency's draft single programming document before its submission to the Commission for its opinion, and the Agency's single programming document by a majority of two-thirds of members entitled to vote and in accordance with Article 154;

(f) assess and adopt a consolidated annual activity report on the Agency's activities and send it by 1 July each year to the European Parliament, the Council, the Commission and the Court of Auditors. The consolidated annual activity report shall be made public;

(g) adopt the annual budget of the Agency by a majority of two-thirds of the members entitled to vote and in accordance with Article 154;

(h) adopt the financial rules applicable to the Agency in accordance with Article 155;

(i) exercise, with respect to the staff of the Agency, the powers conferred by Regulation No 31 by the Council of the European Economic Community, and Regulation No 11 and by the Council of the European Atomic Energy Community ('Staff Regulations' and 'Conditions of Employment of Other Servants')[39] on the Appointing Authority and on the Authority Empowered to Conclude a Contract of Employment ('the appointing authority powers');

(j) adopt implementing rules for giving effect to the Staff Regulations and the Conditions of Employment of Other Servants in accordance with Article 110 of the Staff Regulations;

(k) develop contacts with stakeholders and stipulate the conditions applicable as mentioned in Article 163;

(l) adopt an anti-fraud strategy, proportionate to risks of fraud taking into account the costs and benefits of the measures to be implemented;

(m) ensure adequate follow-up to findings and recommendations stemming from the internal or external audit reports and evaluations, as well as from investigations of the European Anti-fraud Office ('OLAF') and the European Public Prosecutor's Office ('EPPO');

(n) adopt rules to ensure the availability to the public of information concerning the authorisation or supervision of medicinal products for human use as mentioned in Article 166;

(o) adopt an efficiency gains and synergies strategy;

(p) adopt a strategy for cooperation with third countries or international organisations;

(q) adopt a strategy for the organisational management and internal control systems.

The Management Board shall adopt, in accordance with Article 110 of the Staff Regulations, a decision based on Article 2(1) of the Staff Regulations and on Article 6 of the Conditions of Employment of Other Servants, delegating relevant appointing authority powers to the Executive Director and defining the conditions under which that delegation of powers can be suspended. The Executive Director shall be authorised to sub-delegate those powers.

---

[39] Regulation No 31 (EEC), 11 (EAEC) by the Council of the European Economic Community and by the Council of the European Atomic Energy Community, laying down the Staff Regulations of Officials and the Conditions of Employment of Other Servants of the European Economic Community and the European Atomic Energy Community (OJ 45, 14.6.1962, p. 1385).

Where exceptional circumstances so require, the Management Board may, by way of a decision, temporarily suspend the delegation of the appointing authority powers to the Executive Director and those sub-delegated by the latter and exercise them itself or delegate them to one of its members or to a staff member other than the Executive Director.

Article 145

Executive Director

1. The Executive Director shall be engaged as a temporary agent of the Agency under Article 2, point (a), of the Conditions of Employment of Other Servants.

2. The Executive Director shall be appointed by the Management Board from a list of candidates proposed by the Commission following an open and transparent selection procedure.

   For the purpose of concluding the contract with the Executive Director, the Agency shall be represented by the Chairperson of the Management Board.

   Before appointment, the candidate nominated by the Management Board shall be immediately invited to make a statement to the European Parliament and to answer any questions put by its Members.

3. The term of office of the Executive Director shall be five years. By the end of that period the Commission shall undertake an assessment that takes into account an evaluation of the Executive Director's performance and the Agency's future tasks and challenges.

4. The Management Board, acting on a proposal from the Commission that takes into account the assessment referred to in paragraph 3, may extend the term of office of the Executive Director once, for no more than five years.

   An Executive Director whose term of office has been extended may not participate in another selection procedure for the same post at the end of the overall period.

5. The Executive Director may be removed from office only upon a decision of the Management Board acting on a proposal from the Commission.

6. The Management Board shall reach decisions on appointment, extension of the term of office or removal from office of the Executive Director on the basis of a two-thirds majority of its members with voting rights.

7. The Executive Director will be assisted by a Deputy Executive Director. If the Executive Director is absent or indisposed, the Deputy Executive Director shall take their place.

8. The Executive Director shall manage the Agency. The Executive Director shall be accountable to the Management Board. Without prejudice to the powers of the Commission and of the Management Board, the Executive Director shall be independent in the performance of their duties and shall neither seek nor take instructions from any government or from any other body.

9. The Executive Director shall report to the European Parliament on the performance of their tasks when invited to do so. The Council may invite the Executive Director to report on the performance of those tasks.

10. The Executive Director shall be the legal representative of the Agency. The Executive Director shall be responsible for:

    (a) the day-to-day administration of the Agency;

(b) implementing decisions adopted by the Management Board;

(c) managing all the Agency resources necessary for conducting the activities of the Committees referred to in Article 142, including making available appropriate scientific and technical support to those Committees, and for making available appropriate technical support to the coordination group;

(d) ensuring that the time-limits laid down in Union legal acts for the adoption of opinions by the Agency are complied with;

(e) ensuring appropriate coordination between the Committees referred to in Article 142 and, where necessary, between those Committees and the coordination group or other working groups of the Agency;

(f) the preparation of the draft statement of estimates of the Agency's revenue and expenditure, and execution of its budget;

(g) the preparation of the draft single programming document and the submission it to the Management Board after consulting the Commission;

(h) implementing the single programming document and report to the Management Board on its implementation;

(i) preparing the Agency's consolidated annual activity report on the Agency's activities and presenting it to the Management Board for assessment and adoption;

(j) all staff matters;

(k) providing the secretariat for the Management Board;

(l) without prejudice to the competences of OLAF and EPPO, protecting the financial interests of the Union by applying preventive measures against fraud, corruption and any other illegal activities, by effective checks and, if irregularities are detected, by recovering amounts wrongly paid and, where appropriate, by imposing effective, proportionate and dissuasive administrative and financial penalties;

(m) reporting, on the basis of key performance indicators agreed by the Management board, on the IT infrastructure developed by the Agency by means of implementation of legislation, in term of timing, budgetary compliance and quality.

11. Each year the Executive Director shall submit a draft report covering the activities of the Agency in the previous year and a draft work programme for the coming year to the Management Board for approval, making a distinction between the Agency's activities concerning medicinal products for human use, those concerning herbal medicinal products and those concerning veterinary medicinal products.

The draft report covering the activities of the Agency in the previous year shall include information about the number of applications evaluated by the Agency, the time taken for completion of the evaluation, and the medicinal products for human use and veterinary medicinal products authorised, rejected or withdrawn.

Article 146

Scientific Committees – General provisions

1. The scientific committees shall be responsible for providing the scientific opinions or recommendations of the Agency, each within their own spheres of competence, and shall have the possibility, where necessary of organising public hearings.

2. The membership of the scientific committees shall be made public. When each appointment is published, the professional qualifications of each member shall be specified.

3. The Executive Director of the Agency or their representative and representatives of the Commission shall be entitled to attend all meetings of the scientific committees referred to in Article 142, working parties and scientific advisory groups and all other meetings convened by the Agency or its scientific committees.

4. Members of the scientific committees and experts responsible for evaluating medicinal products and nominated by Member States shall rely on the scientific evaluation and resources available to national competent authorities responsible for marketing authorisation, and on external experts proposed by Member States or selected by the Agency. Each competent national authority shall monitor the scientific level and independence of the evaluation carried out and facilitate the activities of nominated members of the Committees and experts. Member States shall refrain from giving those members and experts any instruction which is incompatible with their own individual tasks or with the tasks and responsibilities of the Agency.

5. The members of the scientific committees may be accompanied by experts in specific scientific or technical fields.

6. When preparing any opinion or recommendation, the scientific committees shall use their best endeavours to reach a scientific consensus. If such a consensus cannot be reached, the opinion shall consist of the position of the majority of members and divergent positions, with the grounds on which they are based.

7. The Committee for Medicinal Products for Human Use may, if they consider it appropriate, seek guidance on important questions of a general scientific or ethical nature.

8. The scientific committees and any working parties and scientific advisory groups established in accordance with this Article shall in general matters establish contacts, on an advisory basis, with parties concerned with the use of medicinal products for human use, in particular patient and consumer organisations and healthcare professionals' associations. For that purpose working groups of patient and consumer organisations and healthcare professionals' associations shall be established by the Agency. They shall ensure a fair representation of healthcare professionals, patients and consumers covering a wide range of experience and disease areas, including orphan, paediatric and geriatric diseases and advanced therapy medicinal products, and a broad geographical range.

   Rapporteurs appointed by the scientific committees may, on an advisory basis, establish contacts with representatives of patient organisations and healthcare professionals' associations relevant to the therapeutic indication of the medicinal product for human use.

9. The Committee for Veterinary Medicinal Products shall operate in accordance with Regulation (EU) No 2019/6 and paragraphs 1, 2 and 3.

Article 147

Conflict of interest

1. Members of the Management Board, members of the committees, rapporteurs and experts shall not have financial or other interests in the pharmaceutical industry which could affect their impartiality. They shall undertake to act in the public interest and in an independent manner, and shall make an annual declaration of their financial interests. All indirect

interests which could relate to this industry shall be entered in a register held by the Agency which is accessible to the public, on request, at the Agency's offices.

The Agency's code of conduct shall provide for the implementation of this Article with particular reference to the acceptance of gifts.

2. Members of the Management Board, members of the committees, rapporteurs and experts who participate in meetings or working groups of the Agency shall declare, at each meeting, any specific interests which could be considered to be prejudicial to their independence with respect to the items on the agenda. These declarations shall be made available to the public.

Article 148

Committee for Medicinal Products for Human Use activities

1. The Committee for Medicinal Products for Human Use shall be responsible for drawing up the opinion of the Agency on any matter concerning the admissibility of the files submitted in accordance with the centralised procedure, the granting, variation, suspension or revocation of an authorisation to place a medicinal product for human use on the market in accordance with the provisions of this Chapter, and pharmacovigilance. For the fulfilment of its pharmacovigilance tasks, including the approval of risk management systems and monitoring their effectiveness provided for under this Regulation, the Committee for Medicinal Products for Human Use shall rely on the scientific assessment and recommendations of the Pharmacovigilance Risk Assessment Committee referred to in Article 142, point (e).

2. In addition to their task of providing objective scientific opinions to the Union and Member States on the questions which are referred to them, the members of the Committee for Medicinal Products for Human Use shall ensure that there is appropriate coordination between the tasks of the Agency and the work of competent national authorities, including the consultative bodies concerned with the marketing authorisation.

3. The Committee for Medicinal Products for Human Use shall be composed of the following:

   (a) one member and one alternate member appointed by each Member State, in accordance with paragraph 6;

   (b) four members and one alternate members appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent healthcare professionals;

   (c) four members and four alternate members appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent patient organisations.

4. The Committee for Medicinal Products for Human Use may co-opt a maximum of five additional members chosen on the basis of their specific scientific competence. Those members shall be appointed for a term of three years, which may be renewed, and shall not have alternates.

   With a view to the co-opting of such members, the Committee for Medicinal Products for Human Use shall identify the specific complementary scientific competence of the additional member or members. Co-opted members shall be chosen among experts nominated by Member States or the Agency.

5. The alternates shall represent and vote for the members in their absence and may also be appointed to act as rapporteurs in accordance with Article 152.

Members and alternates shall be chosen for their role and experience in the evaluation of medicinal products for human use as appropriate and shall represent the competent authorities of the Member States.

6. The members and alternate members of the Committee for Medicinal Products for Human Use shall be appointed on the basis of their relevant expertise in the assessment of medicinal products which should cover all types of medicinal products covered by [revised Directive 2001/83/EC] and this Regulation and which include medicinal products for rare and paediatric diseases, advance therapy medicinal products, biological and biotechnological products, in order to guarantee the highest levels of specialist qualifications and a broad spectrum of relevant expertise. The Member States shall cooperate in order to ensure that the final composition of the Committee for Medicinal Products for Human Use provides appropriate and balanced coverage of all scientific areas relevant to its tasks taking into account scientific developments and new types of medicinal products. For this purpose, Member States shall liaise with the Management Board and the Commission.

7. The members and alternate members of the Committee for Medicinal Products for Human Use shall be appointed for a term of thee years, which may be renewed following the procedures referred to in paragraph 6. The Committee shall elect its chairperson and vice-chairperson from among its members for a term of 3 years, which may be prolonged once.

8. The Committee for Medicinal Products for Human Use shall establish its own rules of procedure.

These rules shall, in particular, lay down:

(a) procedures for appointing and replacing the chairperson;

(b) procedures relating to working parties and scientific advisory groups; and

(c) a procedure for the urgent adoption of opinions, particularly in relation to the provisions of this Regulation on market surveillance and pharmacovigilance.

They shall enter into force after receiving a favourable opinion from the Commission and the Management Board.

Article 149

Pharmacovigilance Risk Assessment Committee activities

1. The mandate of the Pharmacovigilance Risk Assessment Committee shall cover all aspects of the risk management of the use of medicinal products for human use including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product for human use, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit.

2. The Pharmacovigilance Risk Assessment Committee shall be composed of the following:

(a) one member and one alternate member appointed by each Member State, in accordance with paragraph 3;

(b) six members appointed by the Commission, with a view to ensuring that the relevant expertise is available within the Committee, including clinical pharmacology and pharmacoepidemiology, on the basis of a public call for expressions of interest;

(c) two members and two alternate members appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent healthcare professionals;

(d) two members and two alternate members appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent patient organisations.

The alternate members shall represent and vote for the members in their absence. The alternate members referred to in point (a) may be appointed to act as rapporteurs in accordance with Article 152.

3. A Member State may delegate its tasks in the Pharmacovigilance Risk Assessment Committee to another Member State. Each Member State may represent no more than one other Member State.

4. The members and alternate members of the Pharmacovigilance Risk Assessment Committee shall be appointed on the basis of their relevant expertise in pharmacovigilance matters and risk assessment of medicinal products for human use, in order to guarantee the highest levels of specialist qualifications and a broad spectrum of relevant expertise. For this purpose, Member States shall liaise with the Management Board and the Commission in order to ensure that the final composition of the Committee covers the scientific areas relevant to its tasks.

5. The members and alternate members of the Pharmacovigilance Risk Assessment Committee shall be appointed for a term of 3 years, which may be renewed following the procedures referred to in paragraph 1. The Committee shall elect its chairperson and vice-chairperson from among its members for a term of three years, which may be prolonged once.

Article 150

Scientific working parties and scientific advisory groups

1. The scientific committees referred to in Article 146 may establish scientific working parties and scientific advisory groups in connection with the performance of their tasks.

The scientific committees may rely on scientific working parties for the performance of certain tasks. The scientific committees shall retain the final responsibility for the assessment or any scientific opinion related to these tasks.

Working parties established by the Committee for Veterinary Medicinal Products are governed by Regulation (EU) 2019/6.

2. The Committee for Human Medicinal Products shall establish for the evaluation of specific types of medicinal products or treatments, working parties with scientific expertise in the fields of pharmaceutical quality, methodologies, non-clinical and clinical evaluations.

For the provision of scientific advice the Committee for Human Medicinal Products shall establish a scientific advice working party.

The Committee may establish an Environmental Risk Assessment working party and other scientific working parties, as necessary.

3. The composition of the working party and the selection of members shall be based on the following criteria:

(a) a high level of scientific expertise;

(b) meeting the needs for the specific multi-disciplinary expertise of the working party to which they will be appointed.

The majority of the members of the working parties shall consist of experts from the competent authorities of the Member States. Where appropriate, the Committee for Human Medicinal Products may, following consultation with the Management Board, set a minimum number of experts from the competent authorities in a working party.

4. Competent authorities of the Member States that are not represented in a working party may request to attend meetings of working parties as an observer.

5. The Agency shall make documents discussed in working parties accessible to all competent authorities of the Member States.

6. When establishing working parties and scientific advisory groups, the scientific committees shall in their rules of procedures provide for:

(a) the appointment of members of these working parties and scientific advisory groups on the basis of the lists of experts referred to in Article 151(2); and

(b) consultation of these working parties and scientific advisory groups.

Article 151

Scientific experts

1. The Agency or any of the committees referred to in Article 142 may use the services of experts and service providers for the discharge of specific tasks for which they are responsible.

2. Member States shall transmit to the Agency the names of national experts with proven experience in the evaluation of medicinal products for human use and veterinary medicinal products who, taking into account conflicts of interest pursuant to Article 147, would be available to serve on working parties or scientific advisory groups of any of the committees referred to in Article 142, together with an indication of their qualifications and specific areas of expertise.

3. Where necessary, for the nomination of other experts the Agency may publish a call for expression of interest after endorsement by the Management Board of the necessary criteria and fields of expertise, in particular to ensure a high level of public health and animal protection.

The Management Board shall adopt the appropriate procedures on a proposal from the Executive Director.

4. The Agency shall establish and maintain a pool of accredited experts. That expert pool shall include the national experts referred to in paragraph 2 and any other experts appointed by the Agency or the Commission, and shall be updated.

5. Accredited experts shall have access to training provided by the Agency, as appropriate.

6. Rapporteurs of any of the committees referred to in Article 142 may use the services of accredited experts for the fulfilment of their tasks in accordance with Article 152. Any

remuneration of such accredited expert shall be deducted from the remuneration due to the rapporteurs.

7. The remuneration of experts and service providers for services used by the Agency under paragraph 1 shall be financed through the Agency's budget, in accordance with the financial rules applicable to the Agency.

Article 152

Rapporteurship

1. Where, in accordance with this Regulation, any of the Committees referred to in Article 142 is required to evaluate a medicinal product for human use, it shall appoint one of its members to act as rapporteur, taking into account existing expertise in the Member State. The Committee concerned may appoint a second member to act as co-rapporteur.

   A member of a Committee shall not be appointed rapporteur for a particular case if they declare, in accordance with Article 147 any interest that might be, or might be perceived as, prejudicial to the impartial assessment of that case. The Committee concerned may replace the rapporteur or co-rapporteur by another member at any time, if they are unable to fulfil their duties within the prescribed time limits, or if an actual or potential prejudicial interest is detected.

   A rapporteur appointed for that purpose by the Pharmacovigilance Risk Assessment Committee shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use or the Reference Member State for the medicinal product for human use concerned.

   When consulting the scientific advisory groups referred to in Article 150, the Committee shall forward to them the draft assessment report or reports drawn up by the rapporteur or the co-rapporteur. The opinion issued by the scientific advisory group shall be forwarded to the chairperson of the relevant committee in such a way as to ensure that the deadlines laid down in Article 6 are met.

   The substance of the opinion shall be included in the assessment report published pursuant to Article 16(3).

2. Without prejudice to Article 151(7), the provision of services by rapporteurs or experts shall be governed by a written contract between the Agency and the person concerned, or where appropriate between the Agency and its employer.

   The person concerned, or their employer, shall be remunerated in accordance with [a scale of fees to be included in the financial arrangements established by the Management Board/mechanism under the new fee legislation].

   The first and second subparagraphs shall also apply:

   (a) to the services provided by the chairpersons of the scientific committees of the Agency; and

   (b) to the work of rapporteurs in the coordination group as regards the fulfilment of its tasks in accordance with Articles 108, 110, 112, 116 and 121 of [revised Directive 2001/83/EC].

Article 1

Methods to determine added therapeutic value

At the request of the Commission, the Agency shall, in respect of authorised medicinal products for human use, collect any available information on methods that Member States' competent authorities use to determine the added therapeutic value that any new medicinal product for human use provides.

SECTION 3

FINANCIAL PROVISIONS

Article 154

Adoption of the budget of the Agency

1. Estimates of all the revenue and expenditure of the Agency shall be prepared for each financial year, corresponding to the calendar year, and shall be shown in the budget of the Agency.

2. The revenue and expenditure shown in the budget shall be in balance.

3. The Agency's revenue shall consist of:

   (a) a contribution from the Union;

   (b) a contribution from third countries participating in the work of the Agency with which the Union has concluded international agreements for that purpose;

   (c) fees paid by undertakings and entities not engaged in an economic activity:

      (i) for obtaining and maintaining Union marketing authorisations for medicinal products for human use and for veterinary medicinal products and for other services provided by the Agency, as provided for in this Regulation and in Regulation (EU) 2019/6; and

      (ii) for services provided by the coordination group as regards the fulfilment of its tasks in accordance with Articles 108, 110, 112, 116 and 121 of [revised Directive 2001/83/EC];

   (d) charges for other services provided by the Agency;

   (e) Union funding in the form of grants for participation in research and assistance projects, in accordance with the Agency's financial rules referred to in Article 155(11) and with the provisions of the relevant instruments supporting the policies of the Union.

   The European Parliament and the Council ('the budgetary authority') shall re-examine, when necessary, the level of the Union contribution, referred to in the first subparagraph, point (a), on the basis of an evaluation of needs and by taking account of the level of revenue provided by the sources referred to in the first subparagraph, points (c), (d) and (e).

4. Activities relating to the assessment of marketing authorisation applications, subsequent variations, pharmacovigilance, to the operation of communications networks and to market surveillance shall be under the permanent control of the Management Board in order to guarantee the independence of the Agency. This shall not preclude the Agency from charging fees to marketing authorisation holders for performing these activities by the Agency on the condition that its independence is strictly guaranteed.

5. The expenditure of the Agency shall include staff remuneration, administrative and infrastructure costs, and operational expenditure. In respect of operational expenditure, budgetary commitments for actions which extend over more than one financial year may be broken down over several years into annual instalments, as necessary.

The Agency may award grants related to the fulfilment of the tasks incumbent upon it under this Regulation or other relevant Union legal acts or related to the fulfilment of other entrusted tasks.

6. Each year the Management Board, on the basis of a draft drawn up by the Executive Director, shall produce an estimate of revenue and expenditure for the Agency for the following financial year. That estimate, which shall include a draft establishment plan, shall be forwarded by the Management Board to the Commission by 31 March at the latest.

7. The estimate shall be forwarded by the Commission to the budgetary authority together with the preliminary draft general budget of the European Union.

8. On the basis of the estimate, the Commission shall enter in the preliminary draft general budget of the European Union the estimates it deems necessary for the establishment plan and the amount of the subsidy to be charged to the general budget, which it shall place before the budgetary authority in accordance with Article 272 of the Treaty.

9. The budgetary authority shall authorise the appropriations for the subsidy to the Agency.

The budgetary authority shall adopt the establishment plan for the Agency.

10. The budget shall be adopted by the Management Board. It shall become final following final adoption of the general budget of the European Union. Where appropriate, it shall be adjusted accordingly.

11. Any modification of the establishment plan and of the budget shall be the subject of an amending budget, which is forwarded for the purposes of information to the budgetary authority.

12. The Management Board shall, as soon as possible, notify the budgetary authority of its intention to implement any project which may have significant financial implications for the funding of its budget, in particular any projects relating to property such as the rental or purchase of buildings. It shall inform the Commission thereof.

Where a branch of the budgetary authority has notified its intention to deliver an opinion, it shall forward its opinion to the Management Board within a period of six weeks from the date of notification of the project.

Article 155

Implementation of the Agency's budget

1. The Executive Director shall implement the budget of the Agency in accordance with Regulation (EU, Euratom) 2018/1046 of the European Parliament and of the Council[40].

[40] Regulation (EU, Euratom) 2018/1046 of the European Parliament and of the Council of 18 July 2018 on the financial rules applicable to the general budget of the Union, amending Regulations (EU) No 1296/2013, (EU) No 1301/2013, (EU) No 1303/2013, (EU) No 1304/2013, (EU) No 1309/2013, (EU) No 1316/2013, (EU) No 223/2014, (EU) No 283/2014, and Decision No 541/2014/EU and repealing Regulation (EU, Euratom) No 966/2012 (OJ L 193, 30.7.2018, p. 1).

2. By 1 March of financial year n+1, the Agency's accounting officer shall send the provisional accounts for year n to the Commission's accounting officer and to the Court of Auditors.

3. By 31 March of financial year n+1, the Executive Director shall send the report on the budgetary and financial management for year n to the European Parliament, to the Council, to the Commission and to the Court of Auditors.

4. By 31 March of financial year n+1, the Commission's accounting officer shall send the Agency's provisional accounts for year n, consolidated with the Commission's provisional accounts, to the Court of Auditors.

   On receipt of the Court of Auditors' observations on the Agency's provisional accounts pursuant to Article 246 of Regulation (EU, Euratom) 2018/1046, the Agency's accounting officer shall draw up the Agency's final accounts and the Executive Director shall submit them to the Management Board for an opinion.

5. The Management Board shall deliver an opinion on the Agency's final accounts for year n.

6. The Agency's accounting officer shall, by 1 July of financial year n+1, send the final accounts, together with the Management Board's opinion, to the European Parliament, to the Council, to the Court of Auditors and to the Commission's accounting officer.

7. The final accounts for year n shall be published in the *Official Journal of the European Union* by 15 November of financial year n+1.

8. The Executive Director shall send to the Court of Auditors a reply to its observations by 30 September of financial year n+1. The Executive Director shall also send that reply to the Management Board.

9. The Executive Director shall submit to the European Parliament, at the latter's request, any information required for the smooth application of the discharge procedure for the financial year concerned, as laid down in Article 261(3) of Regulation (EU, Euratom) 2018/1046.

10. The European Parliament, upon a recommendation from the Council, shall, before 15 May of financial year n+2, give a discharge to the Executive Director in respect of the implementation of the budget for year n.

11. The financial rules applicable to the Agency shall be adopted by the Management Board after the Commission has been consulted. They shall not depart from Commission Delegated Regulation (EU) 2019/715[41] unless specifically required for the Agency's operation and with the Commission's prior consent.

Article 156

Fraud prevention

1. In order to combat fraud, corruption and other unlawful activities, the Regulation (EU, Euratom) No 883/2013 of the European Parliament and of the Council[42] shall apply without restriction.

---

[41] Commission Delegated Regulation (EU) 2019/715 of 18 December 2018 on the framework financial regulation for the bodies set up under the TFEU and Euratom Treaty and referred to in Article 70 of Regulation (EU, Euratom) 2018/1046 of the European Parliament and of the Council (OJ L 122, 10.5.2019, p. 1).

[42] Regulation (EU, Euratom) No 883/2013 of the European Parliament and of the Council of 11 September 2013 concerning investigations conducted by the European Anti-Fraud Office (OLAF) and repealing Regulation

2. The Agency shall accede to the Interinstitutional Agreement of 25 May 1999 between the European Parliament, the Council of the European Union and the Commission of the European Communities[43] and shall adopt, without delay, the appropriate provisions applicable to all the employees of the Agency using the template set out in the Annex to that Agreement.

3. The European Court of Auditors shall have the power of audit, on the basis of documents and on the spot, over all grant beneficiaries, contractors and subcontractors who have received Union funds from the Agency.

4. OLAF may carry out investigations, including on-the-spot checks and inspections with a view to establishing whether there has been fraud, corruption or any other illegal activity affecting the financial interests of the Union in connection with a grant or a contract funded by the Agency, in accordance with the provisions and procedures laid down in Regulation (EU, Euratom) No 883/2013 and Council Regulation (Euratom, EC) No 2185/96[44].

5. Working agreements with third countries and international organisations, contracts, grant agreements and grant decisions of the Agency shall contain provisions expressly empowering the European Court of Auditors and OLAF to conduct such audits and investigations, according to their respective competences.

6. In accordance with Council Regulation (EU) 2017/1939[45], the EPPO may investigate and prosecute fraud and other illegal activities affecting the financial interests of the Union as provided for in Directive (EU) 2017/1371 of the European Parliament and of the Council[46].

SECTION 4

GENERAL PROVISIONS GOVERNING THE AGENCY

Article 157

Liability

1. The contractual liability of the Agency shall be governed by the law applicable to the contract in question. The Court of Justice of the European Union shall have jurisdiction pursuant to any arbitration clause contained in a contract concluded by the Agency.

2. In the case of non-contractual liability, the Agency shall, in accordance with the general principles common to the laws of the Member States, make good any damage caused by it or by its staff in the performance of their duties.

(EC) No 1073/1999 of the European Parliament and of the Council and Council Regulation (Euratom) No 1074/1999 (OJ L 248, 18.9.2013, p. 1).

43 Interinstitutional Agreement of 25 May 1999 between the European Parliament, the Council of the European Union and the Commission of the European Communities concerning internal investigations by the European Anti-fraud Office (OLAF) (OJ L 136, 31.5.1999, p. 15).

44 Council Regulation (Euratom, EC) No 2185/96 of 11 November 1996 concerning on-the-spot checks and inspections carried out by the Commission in order to protect the European Communities' financial interests against fraud and other irregularities (OJ L 292, 15.11.1996, p. 2).

45 Council Regulation (EU) 2017/1939 of 12 October 2017 implementing enhanced cooperation on the establishment of the European Public Prosecutor's Office ('the EPPO') (OJ L 283, 31.10.2017, p. 1).

46 Directive (EU) 2017/1371 of the European Parliament and of the Council of 5 July 2017 on the fight against fraud to the Union's financial interests by means of criminal law (OJ L 198, 28.7.2017, p. 29).

The Court of Justice shall have jurisdiction in any dispute relating to compensation for any such damage.

3. The personal liability of its staff towards the Agency shall be governed by the provisions laid down in the Staff Regulations or Conditions of Employment of Other Servants applicable to them.

Article 158

Access to documents

Regulation (EC) No 1049/2001 shall apply to documents held by the Agency.

The Agency shall set up a register pursuant to Article 2(4) of Regulation (EC) No 1049/2001 to make available all documents that are publicly available pursuant to this Regulation.

The Management Board shall adopt the arrangements for implementing Regulation (EC) No 1049/2001.

Decisions taken by the Agency pursuant to Article 8 of Regulation (EC) No 1049/2001 may give rise to the lodging of a complaint with the Ombudsman or form the subject of an action before the Court of Justice, under the conditions laid down in Article 228 and Article 263 of the Treaty respectively.

Article 159

Privileges

Protocol No 7 on the Privileges and Immunities of the European Union annexed to the Treaty on the Functioning of the European Union shall apply to the Agency and its staff.

Article 160

Staff

The Staff Regulations and the rules adopted by agreement between the institutions of the Union for giving effect to those Staff Regulations and Conditions of Employment of Other Servants shall apply to the staff of the Agency.

The Agency may make use of seconded national experts or other staff not employed by the Agency.

The Management Board, in agreement with the Commission, shall adopt the necessary implementing provisions.

Article 161

Security rules on the protection of classified and sensitive non-classified information

The Agency shall adopt own security rules equivalent to the Commission's security rules for protecting European Union Classified Information (EUCI) and sensitive non-classified information, as set out in Commission Decisions (EU, Euratom) 2015/443[47] and 2015/444[48]. The security rules

[47] Commission Decision (EU, Euratom) 2015/443 of 13 March 2015 on Security in the Commission (OJ L 72, 17.3.2015, p. 41).

[48] Commission Decision (EU, Euratom) 2015/444 of 13 March 2015 on the security rules for protecting EU classified information (OJ L 72, 17.3.2015, p. 53).

of the Agency shall cover, inter alia, provisions for the exchange, processing and storage of such information.

Members of the Management Board, the Executive Director, members of the committees, external experts participating in ad hoc working groups, and members of the staff of the Agency shall comply with the confidentiality requirements under Article 339 TFEU, even after their duties have ceased.

The Agency may take the necessary measures to facilitate the exchange of information relevant to its tasks with the Commission and the Member States and, where appropriate, the relevant Union institutions, bodies, offices and agencies. Any administrative arrangements concluded to that end with regard to the sharing of EU classified information (EUCI) or, in the absence of such arrangements, any exceptional ad hoc release of EUCI, shall have received the Commission's prior approval.

Article 162

Consultation process

1. The Agency shall establish a consultation process with relevant national authorities or bodies for the exchange of information and pooling of knowledge on general issues of scientific or technical nature related to the tasks of the Agency, in particular guidelines on unmet medical needs and the design of clinical trials, other studies and the generation of evidence along the life cycle of medicinal products.

   The consultation process shall include bodies responsible for health technology assessment as referred to in Regulation (EU) 2021/2282 and national bodies responsible for pricing and reimbursement.

   The conditions of participation shall be set by the Management Board in agreement with the Commission.

2. The Agency may extend the consultation process to patients, medicine developers, healthcare professionals, industries or other stakeholders, as relevant.

Article 163

Contacts with civil society representatives

The Management Board shall, in agreement with the Commission, develop appropriate contacts between the Agency and the representatives of the industry, consumers and patients and the healthcare professions. These contacts may include the participation of observers in certain aspects of the Agency's work, under conditions determined beforehand by the Management Board, in agreement with the Commission.

Article 164

Support to SMEs and to not-for profit entities

1. The Agency shall ensure that micro, small and medium-sized enterprises ('SMEs') and not-for-profit entities are offered a support scheme.

2. The support scheme shall be comprised of regulatory, procedural and administrative support and reduction, deferral or waivers of fees.

3. The scheme shall cover the various steps involved in pre-authorisation procedures, and in particular scientific advice, the submission of the marketing authorisation application, and the post-authorisation procedures.

4. SMEs shall benefit from the incentives laid down in Commission Regulation (EC) No 2049/2005 and [revised Council Regulation (EC) No 297/95][49].

5. For not-for-profit entities, the Commission shall adopt specific provisions clarifying the definitions, establishing waivers, reductions or deferrals of fees, as appropriate, in accordance with the procedure referred to in Article 10 and Article 12 of [revised Regulation (EC) No 297/95].

Article 165

Transparency

To ensure an appropriate level of transparency, the Management Board shall, on the basis of a proposal by the Executive Director and in agreement with the Commission, adopt rules to ensure the availability to the public of regulatory, scientific or technical information concerning the authorisation or supervision of medicinal products for human use which is not of a confidential nature.

The internal rules and procedures of the Agency, its committees and its working groups shall be made available to the public at the Agency and on the Internet.

The Agency may engage in communication activities on its own initiative within its field of competence. The allocation of resources to communication activities shall not be detrimental to the effective exercise of the tasks of the Agency. Communication activities shall be carried out in accordance with relevant communication and dissemination plans adopted by the Management Board.

Article 166

Personal health data

1. To support its public health tasks and in particular the evaluation and monitoring medicinal products or the preparation of regulatory decisions and scientific opinions, the Agency may process personal health data, from sources other than clinical trials, for the purpose of improving the robustness of its scientific assessment or verifying claims of the applicant or marketing authorisation holder in the context of the evaluation or supervision of medicinal product.

2. The Agency may consider and decide upon additional evidence available, independently from the data submitted by the marketing authorisation applicant or marketing authorisation holder. On that basis, the summary of product characteristics shall be updated if the additional evidence has an impact on the benefit-risk balance of a medicinal product.

3. The Agency shall adopt adequate data governance practices and the required standards to ensure the appropriate use and protection of personal health data, in accordance with this Regulation and Regulation (EU) 2018/1725.

[49] Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products (OJ L 35, 15.2.1995, p. 1).

Article 167

Protection against cyber attacks

The Agency shall equip itself with a high level of security controls and processes against cyber attacks, cyber espionage and other data breaches to ensure the protection of health data and the normal functioning of the Agency at all times, especially during public health emergencies or major events at Union level.

For the purposes of the first subparagraph, the Agency shall actively identify and implement cybersecurity best practices adopted within Union institutions, bodies, offices and agencies for preventing, detecting, mitigating, and responding to cyber attacks.

Article 168

Confidentiality

1. Unless otherwise provided for in this Regulation and without prejudice to Regulation (EC) No 1049/2001 and Directive (EU) 2019/1937 of the European Parliament and of the Council[50], and existing national provisions and practices in the Member States on confidentiality, all parties involved in the application of this Regulation shall respect the confidentiality of information and data obtained in carrying out their tasks in order to protect the commercially confidential information and trade secrets of natural or legal persons in accordance with Directive (EU) 2016/943 of the European Parliament and of the Council[51], including intellectual property rights.
2. Without prejudice to paragraph 1, all parties involved in the application of this Regulation shall ensure that no commercially confidential information is shared in a way which has the potential to enable undertakings to restrict or distort competition within the meaning of Article 101 TFEU.
3. Without prejudice to paragraph 1, information exchanged on a confidential basis between competent authorities of the Member States and between competent authorities of the Member States and the Commission and the Agency shall not be disclosed without the prior agreement of the authority from which that information originates.
4. Paragraphs 1, 2 and 3 do not affect the rights and obligations of the Commission, the Agency, Member States or other actors identified in this Regulation with regard to the exchange of information and the dissemination of warnings, nor do they affect the obligations of the persons concerned to provide information under criminal law.
5. The Commission, the Agency, and Member States may exchange commercially confidential information with regulatory authorities of third countries with which they have concluded bilateral or multilateral confidentiality arrangements.

Article 169

Processing of personal data

---

50 Directive (EU) 2019/1937 of the European Parliament and of the Council of 23 October 2019 on the protection of persons who report breaches of Union law (OJ L 305, 26.11.2019, p. 17).

51 Directive (EU) 2016/943 of the European Parliament and of the Council of 8 June 2016 on the protection of undisclosed know-how and business information (trade secrets) against their unlawful acquisition, use and disclosure (OJ L 157, 15.6.2016, p. 1).

1. The Agency may process personal data, including personal health data, for the performance of its tasks as referred to in Article 135, in particular for the purpose of improving the robustness of its scientific assessment or verifying claims of the applicant or marketing authorisation holder in the context of the evaluation or supervision of medicinal products.

   Additionally, the Agency may process such data for the performance of regulatory science activities, as defined in paragraph 2, provided that the processing of those personal data:

   (a) is strictly required and duly justified to achieve the objectives of the project or of the horizon scanning activities concerned;

   (b) as regards special categories of personal data, is strictly necessary and subject to appropriate safeguards, which may include pseudonymisation.

2. For the purpose of this Article, 'regulatory science activities' shall mean scientific projects to complement available scientific evidence with regard to diseases or horizontal questions related to medicinal products, to fill evidence gaps that cannot be fully addressed through data in the possession of the Agency, or to support horizon scanning activities.

3. The processing of personal data by the Agency in the context of this Article shall be guided by the principles of transparency, explainability, fairness, and accountability.

4. The Management Board shall establish the general scope for the regulatory science activities in consultation with the Commission and the European Data Protection Supervisor.

5. The Agency shall keep documentation containing a detailed description of the process and of the rationale behind the training, testing and validation of algorithms to ensure transparency of the process and the algorithms, including their compliance with the safeguards provided for in this Article, and to allow for verification of the accuracy of the results based on the use of such algorithms. Upon request, the Agency shall make relevant documentation available to interested parties, including Member States.

6. If the personal data to be processed for the regulatory science activities have been directly provided by a Member State, a Union body, a third country or an international organisation, the Agency shall request authorisation from that provider of data, unless the provider of data has granted its prior authorisation to such processing for the purpose of regulatory science activities, either in general terms or subject to specific conditions.

7. Processing of personal data under this Regulation shall be subject to Regulations (EU) 2016/679 and (EU) 2018/1725, as applicable.

Article 170

Evaluation

1. Not later than [*note to OP = five years after the date of entry into application*], and every 10 years thereafter, the Commission shall commission an evaluation of the Agency's performance in relation to its objectives, mandate, tasks, governance and location(s) in accordance with Commission's guidelines.

2. The evaluation shall, in particular, address the possible need to modify the mandate of the Agency, and the financial implications of any such modification.

3. On the occasion of every second evaluation, there shall be an assessment of the results achieved by the Agency having regard to its objectives, mandate, governance and tasks, including an assessment of whether the continuation of the Agency is still justified with

regard to these objectives, mandate, governance and tasks. This assessment shall also include the experience acquired as a result of the operation of the procedures laid down in this Regulation and in Chapter III, Sections 4 and 5 of [revised Directive 2001/83/EC] on the basis of input from Member States and the Coordination group referred to in Article 37 of [revised Directive 2001/83/EC].

4. The Commission shall report to the European Parliament, the Council and the Management Board on the evaluation findings. The findings of the evaluation shall be made public.

5. By 10 years following the entering into application, the Commission shall assess the application of this Regulation and produce an evaluation report on the progress towards achievement of the objectives contained herein including an assessment of the resources required to implement this Regulation.

CHAPTER XII
GENERAL PROVISIONS

Article 171

Penalties at national level

1. Member States shall lay down the rules on penalties applicable to infringements of this Regulation and shall take all measures necessary to ensure that they are implemented. The penalties provided for shall be effective, proportionate and dissuasive. Member States shall, without delay, notify the Commission of those rules and of those measures and shall notify it, without delay, of any subsequent amendment affecting them.

2. Member States shall inform the Commission immediately of any litigation instituted for infringement of this Regulation.

Article 172

Union penalties

1. The Commission may impose financial penalties in the form of fines or periodic penalty payments on the marketing authorisations holder granted under this Regulation if they fail to comply with any of the obligations laid down in Annex II in connection with the marketing authorisations.

2. The Commission may, insofar as specifically provided for in the delegated acts referred to in paragraph 10, point (b), impose the financial penalties referred to in paragraph 1 on a legal entity or legal entities other than the marketing authorisation holder provided that such entities form part of the same economic entity as the marketing authorisation holder and that such other legal entities:

   (a) exerted a decisive influence over the marketing authorisation holder; or

   (b) were involved in, or could have addressed, such failure to comply with the obligation by the marketing authorisation holder.

3. Where the Agency or a competent authority of a Member State is of the opinion that a marketing authorisation holder has failed to comply with any of the obligations, referred to in paragraph 1, it may request the Commission to investigate whether to impose financial penalties pursuant to that paragraph.

4. In determining whether to impose a financial penalty and in determining its appropriate amount, the Commission shall be guided by the principles of effectiveness, proportionality

and dissuasiveness and take into consideration, where relevant, the seriousness and the effects of the failure to comply with the obligations.

5. For the purposes of paragraph 1, the Commission shall take into account:

   (a) any infringement procedure initiated by a Member State against the same marketing authorisation holder on the basis of the same legal grounds and the same facts;

   (b) any sanctions, including penalties, already imposed on the same marketing authorisation holder on the basis of the same legal grounds and the same facts.

6. Where the Commission finds that the marketing authorisation holder has failed, intentionally or negligently, to comply with its obligations, as referred to in paragraph 1, it may adopt a decision imposing a fine not exceeding 5 % of the marketing authorisation holder's Union turnover in the business year preceding the date of that decision.

   Where the marketing authorisation holder continues to fail to comply with its obligations referred to in paragraph 1, the Commission may adopt a decision imposing periodic penalty payments per day not exceeding 2,5 % of the marketing authorisation holder's average daily Union turnover in the business year preceding the date of that decision.

   Periodic penalty payments may be imposed for a period running from the date of notification of the relevant Commission's decision until the failure to comply with the obligation by the marketing authorisation holder, as referred to in paragraph 1, has been brought to an end.

7. When conducting the investigation on a failure to comply with any of the obligations referred to in paragraph 1, the Commission may cooperate with competent authorities of the Member States and rely on resources provided by the Agency.

8. Where the Commission adopts a decision imposing a financial penalty, it shall publish a concise summary of the case, including the names of the marketing authorisation holders involved and the amounts of and reasons for the financial penalties imposed, having regard to the legitimate interest of the marketing authorisation holders for the protection of their business secrets.

9. The Court of Justice of the European Union shall have unlimited jurisdiction to review decisions whereby the Commission has imposed financial penalties. The Court of Justice of the European Union may cancel, reduce or increase the fine or periodic penalty payment imposed by the Commission.

10. The Commission is empowered to adopt delegated acts in accordance with Article 175 in order to supplement this Regulation by laying down:

    (a) procedures to be applied by the Commission when imposing fines or periodic penalty payments, including rules on the initiation of the procedure, measures of inquiry, rights of the defence, access to file, legal representation and confidentiality;

    (b) further detailed rules on the imposition by the Commission of financial penalties on legal entities other than the marketing authorisation holder;

    (c) rules on duration of procedure and limitation periods;

    (d) elements to be taken into account by the Commission when setting the level of and imposing fines and periodic penalty payments, as well as the conditions and methods for their collection.

CHAPTER XIII
DELEGATED AND IMPLEMENTING ACTS

Article 173

Standing Committee on Medicinal Products for Human Use and examination procedure

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use established by Article 214 of [revised Directive 2001/83/EC]. That committee shall be a committee within the meaning of Regulation (EU) No 182/2011.

2. Where reference is made to this paragraph, Article 5 of Regulation (EU) No 182/2011 shall apply.

3. Where the opinion of the Committee is to be obtained by written procedure and reference is made to this paragraph, that procedure shall be terminated without result only when, within the time-limit for delivery of the opinion, the chair of the Committee so decides.

4. The Standing Committee on Medicinal Products for Human Use shall ensure that its rules of procedure are adapted to the need to make medicinal products swiftly available to patients.

Article 174

Implementing measures related to authorisation and pharmacovigilance activities

1. In order to harmonise electronic transmissions provided for in this Regulation, the Commission may adopt implementing measures covering the format and content of electronic transmissions by marketing authorisation holders.

   Those measures shall take account of the work on international harmonisation carried out in the area and shall, where necessary, be revised to take account of technical and scientific progress. Those measures shall be adopted in accordance with the examination procedure referred to in Article 173(2).

2. In order to harmonise the performance of the pharmacovigilance activities provided for in this Regulation, the Commission shall adopt implementing measures as provided for in Article 214 of [revised Directive 2001/83/EC] covering the following areas:

   (a) the content and maintenance of the pharmacovigilance system master file kept by the marketing authorisation holder;

   (b) the minimum requirements for the quality system for the performance of pharmacovigilance activities by the Agency;

   (c) the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities;

   (d) the minimum requirements for the monitoring of data included in the Eudravigilance database to determine whether there are new risks or whether risks have changed;

   (e) the format and content of electronic transmission of suspected adverse reactions by Member States and marketing authorisation holders;

   (f) the format and content of electronic periodic safety update reports and risk management plans;

(g) the format of protocols, abstracts and final study reports of the post-authorisation safety studies.

Those measures shall take account of the work on international harmonisation carried out in the area of pharmacovigilance and shall, where necessary, be revised to take account of technical and scientific progress. Those measures shall be adopted in accordance with the examination procedure referred to in Article 173(2).

Article 175

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 3(5), 19(8), 21, 47(4), 49(2), 63(2), 67(4), 75(3), 81(4) and 172(10) shall be conferred on the Commission for a period of five years from [date of entry into force]. The Commission shall draw up a report in respect of the delegation of power not later than nine months before the end of the five-year period. The delegation of power shall be tacitly extended for periods of an identical duration, unless the European Parliament or the Council opposes such extension not later than three months before the end of each period.

3. The delegation of power referred to in Articles 3(5), 19(8), 21, 47(4), 49(2), 63(2), 67(4), 75(3), 81(4) and 172(10) 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 21, 19(8), 47(4), 49(2) and 175 shall enter into force only if no objection has been expressed either by the European Parliament or by the Council within a period of two months of notification of that act to the European Parliament and to 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 three months at the initiative of the European Parliament or of the Council.

CHAPTER XIV
AMENDMENTS TO OTHER LEGAL ACTS

Article 176

Amendments to Regulation (EC) No 1394/2007

Regulation (EC) No 1394/2007 is amended as follows:

(1) Articles 8, 17 and 20 to 23 are deleted;

(2) in Article 9(3), the fourth subparagraph is replaced by the following:

‘If the application does not include the results of the assessment, the Agency shall seek an opinion on the conformity of the device part with Annex I to Regulation (EU) 2017/745 of the European Parliament and of the Council* from a notified body identified in conjunction with the applicant, unless the Committee for Medicinal Products for Human Use advised by its experts for medical devices decides that involvement of a notified body is not required.

*Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (OJ L 117, 5.5.2017, p. 1).’

Article 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).

2. The ERA referred to in paragraph 1 shall be conducted in accordance with the principles 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) 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 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 paragraph 5.

6. To obtain and review the additional information referred to in paragraph 6, 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.

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 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[52], Council Directive 96/29/Euratom[53], Directive 2004/23/EC of the European Parliament and of the Council[54], Directive 2002/98/EC of the European Parliament and of the Council[55] and Directive 2010/53/EU of the European Parliament and of the Council[56].

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.'

Article 178

Amendments to Regulation (EU) 2022/123

Regulation (EU) No 2022/123 is amended as follows:

1. In Article 18, the following paragraph (7) is added:

'(7) Where a request has been made in accordance with Article 18(3) of Regulation (EU) 2022/123 and there is an application for a temporary emergency marketing authorisation for the medicinal product concerned in accordance with Article 30 of Regulation [Note to OP: Please fill in with the number of this Regulation]*, the procedure initiated under that Regulation shall prevail.'

* [OP: Insert the full title of that Regulation and the OJ reference, please]

2. Articles 33 and 34 are deleted.

CHAPTER XV
FINAL PROVISIONS

Article 179

Repeals

---

52 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).

53 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).

54 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).

55 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).

56 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).

1. Regulations (EC) No 141/2000, (EC) No 726/2004 and (EC) No 1901/2006 are repealed.

References to the repealed Regulations shall be construed as references to this Regulation and shall be read in accordance with the correlation table in Annex V.

2. Commission Implementing Regulation (EU) No 198/2013[57] is repealed.

Article 180

Transitional provisions

1. The provisions of Article 117 of this Regulation shall also apply to marketing authorisations of medicinal products for human use granted in accordance with Regulation (EC) No 726/2004 and in accordance with Directive 2001/83/EC before [*Note to the OP: Please insert the date = date of entry into application of this Regulation*].

2. The procedures concerning the applications for marketing authorisations for medicinal products for human use that have been validated, in accordance with Article 5 of Regulation (EC) No 726/2004, before [*Note to the OP: Please insert the date = date of entry into application of this Regulation*] and that were pending on [*Note to the OP: Please insert the date = the day before the date of application of this Regulation*] shall be completed in accordance with Article 10 of Regulation (EC) No 726/2004.

3. Procedures concerning imposed post-authorisation studies that were initiated in accordance with Article 10a of Regulation (EC) No 726/2004, before [*Note to the OP: Please insert the date = date of entry into application of this Regulation*] and that were pending on [*Note to the OP: Please insert the date = the day before the date of application of this Regulation*] shall be completed in accordance with Article 20 of this Regulation.

4. By way of derogation, the periods of regulatory protection referred to in Article 29 shall not apply to reference medicinal products for which an application for marketing authorisation has been submitted before [*Note to the OP: Please insert the date of application of this Regulation*]. Article 14(11) of Regulation (EC) No 726/2004 shall continue to apply to them.

5. Orphan designations granted before *[Note to the OP: Please insert the date of application of this Regulation],* entered in and not removed from the Community Register of Orphan Medicinal Products in accordance with Article 5, paragraphs 8 and 12, respectively, of Regulation (EC) No 141/2000 and not granted a marketing authorisation in accordance with Article 7(3) of Regulation (EC) No 141/2000 corresponding to the orphan designation shall be considered to comply with this Regulation and shall be entered in the Register of Designated Orphan Medicinal Products.

6. Orphan designations granted before *[Note to the OP: Please insert the date of application of this Regulation]* which are either removed from the Community Register of Orphan Medicinal Products in accordance with Article 5(12) of Regulation (EC) No 141/2000 or granted a marketing authorisation in accordance with Article 7(3) of Regulation (EC) No 141/2000 shall not be considered as orphan designations and shall not be entered in the Register of Designated Orphan Medicinal Products.

---

[57] Commission Implementing Regulation (EU) No 198/2013 of 7 March 2013 on the selection of a symbol for the purpose of identifying medicinal products for human use that are subject to additional monitoring (OJ L 65, 8.3.2013, p. 17).

7. The 7-year validity of an orphan designation referred to in Article 66 of this Regulation for orphan medicinal products granted before *[Note to the OP: Please insert the date of application of this Regulation],* entered in and not removed from the Community Register of Orphan Medicinal Products in accordance with Article 5 (8) and (12), respectively, of Regulation (EC) No 141/2000 and not granted a marketing authorisation in accordance with those Article 7(3) of Regulation (EC) No 141/2000 corresponding to the orphan designation shall begin to run from *[Note to the OP: Please insert the date of application of this Regulation]*.

8. The procedures concerning orphan designations which were initiated in accordance with Article 5, paragraphs 1, 11 or 12 of Regulation (EC) No 141/2000 before *[Note to the OP: Please insert the date of application of this Regulation]* and were pending on *[OP please insert the date = the day before the date of application]*, shall be completed in accordance with Article 5, paragraphs 1, 11 or 12 of Regulation (EC) No 141/2000 as applicable on [*OP please insert the date = the day before the date of application]*.

9. When a paediatric investigation plan, a waiver or a deferral has been granted in accordance with Regulation (EC) No 1901/2006 before [*Note to the OP: Please insert the date of application of this Regulation*], it shall be considered to comply with this Regulation.

   The procedures concerning the application for a paediatric investigation plan, a waiver or a deferral submitted before [date of entry into application], shall be completed in accordance with Regulation (EC) No 1901/2006.

10. Regulations (EC) No 2141/96, (EC) No 2049/2005, (EC) No 507/2006 and (EC) No 658/2007 shall remain in force and continue to apply unless and until repealed.

11. Regulation (EC) No 1234/2008 shall continue to apply unless and until repealed as regards medicinal products for human use that are covered by Regulation (EC) No 726/2004 and Directive 2001/83/EC and that are not excluded from the scope of Regulation (EC) No 1234/2008 pursuant to Article 23b, paragraphs 4 and 5 of Directive 2001/83/EC.

12. Commission Regulation (EC) No 847/2000[58] shall continue to apply unless and until repealed as regards orphan medicinal products that are covered by this Regulation.

13. By way of derogation from Article [*Duration of application of Chapter III*] vouchers granted until [*Note to OP: insert the date of 15 years after the date of entry into force of this Regulation*] or until the date when the Commission has granted a total of 10 vouchers in accordance with Chapter III, whichever date is the earliest, shall continue to be valid according to the conditions set out in Chapter III.

Article 181

Entry into force

This Regulation shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

It shall apply from [*Note to the OP: Please insert the date of 18 months after its entry into force. The date should be identical to the date for the application of the Directive*].

[58] Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority' (OJ L 103, 28.4.2000, p. 5).

However, Article 67 shall apply from [*Note to the OP: Please insert the date of 2 years after the date of adoption/entry into force/application of this Regulation*].

This Regulation shall be binding in its entirety and directly applicable in the Member States in accordance with the Treaties.

Done at Brussels,

For the European Parliament	*For the Council*
The President	*The President*

LEGISLATIVE FINANCIAL STATEMENT

1. FRAMEWORK OF THE PROPOSAL/INITIATIVE

1.1. Title of the proposal/initiative

1.2. Policy area(s) concerned

1.3. The proposal/initiative relates to:

1.4. Objective(s)

1.4.1. General objective(s)

1.4.2. Specific objective(s)

1.4.3. Expected result(s) and impact

1.4.4. Indicators of performance

1.5. Grounds for the proposal/initiative

1.5.1. Requirement(s) to be met in the short or long term including a detailed timeline for roll-out of the implementation of the initiative

1.5.2. Added value of Union involvement (it may result from different factors, e.g. coordination gains, legal certainty, greater effectiveness or complementarities). For the purposes of this point 'added value of Union involvement' is the value resulting from Union intervention which is additional to the value that would have been otherwise created by Member States alone.

1.5.3. Lessons learned from similar experiences in the past

1.5.4. Compatibility with the Multiannual Financial Framework and possible synergies with other appropriate instruments

1.5.5. Assessment of the different available financing options, including scope for redeployment

1.6. Duration and financial impact of the proposal/initiative

1.7. Management mode(s) planned

2. MANAGEMENT MEASURES

2.1. Monitoring and reporting rules

2.2. Management and control system(s)

2.2.1. Justification of the management mode(s), the funding implementation mechanism(s), the payment modalities and the control strategy proposed

2.2.2. Information concerning the risks identified and the internal control system(s) set up to mitigate them

2.2.3. Estimation and justification of the cost-effectiveness of the controls (ratio of "control costs ÷ value of the related funds managed"), and assessment of the expected levels of risk of error (at payment & at closure)

2.3. Measures to prevent fraud and irregularities

3. ESTIMATED FINANCIAL IMPACT OF THE PROPOSAL/INITIATIVE

3.1. Heading(s) of the multiannual financial framework and expenditure budget line(s) affected

3.2. Estimated financial impact of the proposal on appropriations

3.2.1. Summary of estimated impact on operational appropriations

3.2.2. Estimated output funded with operational appropriations

3.2.3. Summary of estimated impact on administrative appropriations

3.2.4. Compatibility with the current multiannual financial framework

3.2.5. Third-party contributions

3.3. Estimated impact on revenue

LEGISLATIVE FINANCIAL STATEMENT

1. FRAMEWORK OF THE PROPOSAL/INITIATIVE

1.1. Title of the proposal/initiative

Proposal for a revision of Regulation (EC) No 726/2004 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 a European Medicines Agency and Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use and Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products and Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use[1].

1.2. Policy area(s) concerned

Heading 2: Cohesion, Resilience and Values Activity: Health

1.3. The proposal/initiative relates to:

☐ **a new action**

☐ **a new action following a pilot project/preparatory action**[2]

X the extension of an existing action

X a merger or redirection of one or more actions towards another/a new action

---

[1] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 378, 27.12.2006, p. 1).

[2] As referred to in Article 58(2)**, point** (a) or (b)**,** of the Financial Regulation.

1.4. Objective(s)

1.4.1. General objective(s)

The general objective of the revision is to guarantee a high level of public health by ensuring the quality, safety and efficacy of medicines for EU patients and harmonise the internal market.

1.4.2. Specific objective(s)

Specific objectives

1. Promote innovation, in particular for unmet medical needs, including for rare disease patients and children.
2. Create a balanced system for pharmaceuticals in the EU that promotes affordability for health systems while rewarding innovation.
3. Ensure access to innovative and established medicines for patients, with special attention to enhancing security of the supply across the EU.
4. Reduce the environmental impact of the pharmaceutical product life cycle.
5. Reduce the regulatory burden and provide a flexible regulatory framework.

1.4.3. Expected result(s) and impact

Specify the effects which the proposal/initiative should have on the beneficiaries/groups targeted.

The initiative builds on the high level of public health protection and harmonisation achieved for the authorisation of medicines, so that patients across the EU have timely and equitable access and a reliable supply of the medicines they need. Additional obligations and incentives should ensure that patients with rare diseases and children have access to high quality medicines and to safe and effective therapies to address their specific medical needs.

The sector's global competitiveness and innovative power should be supported by striking a balance between giving incentives for innovation, including for unmet medical needs, and measures on access and affordability,. as well as simplification and future-proofing through a framework that is adaptable to scientific and technological change and environmentally sustainable.

1.4.4. Indicators of performance

Specify the indicators for monitoring progress and achievements.

The following core indicators will generate information in a continuous and systematic way on implementation and performance.

For promoting innovation to address unmet medical needs:

– Number of authorised medicines addressing unmet medical needs or high unmet medical needs.

– Number of authorised novel antibiotics

For improving access to patients:

– Average time from authorisation to market launch for newly authorised medicines

– Number of member states in which new medicines launched within 2 years from authorisation

– Number of medicine shortages reported by member states

For environmental impact:

– Presence of medicines residues in the environment

For a flexible and attractive regulatory system:

– Number of authorised medicines with new active substance

– Average assessment time of newly authorised innovative medicines

1.5. Grounds for the proposal/initiative

1.5.1. Requirement(s) to be met in the short or long term including a detailed timeline for roll-out of the implementation of the initiative

Upon the entry into force of the Regulation, the Agency should put in place the framework which will be used to enhance regulatory support and accelerated assessment, to address medicine shortages and supply chain challenges and to strengthen the environmental risk assessment under the marketing authorisation.

Regarding the enhanced regulatory support, the Agency shall set up within 6 months of adoption a coordination mechanism to enable parallel scientific advice with health technology assessment and regulatory bodies for medical devices. Within the same period, the Agency shall create an Academia Office, a secretariat to support not-for-profit entities by providing them free of charge early scientific advice. Furthermore, the Agency shall establish an EU inspectorate within the Agency, to strengthen the network's inspection capacity and deal with emergencies, similar what was needed during the pandemic.

For addressing medicine shortages the Agency shall extend the monitoring and management capacity for all shortages, with a focus on critical shortages, and extend the EMA capacity to support availability of critical medicinal products. This would facilitate appropriate availability and access to medicinal products which may have a serious impact on public health.

The Agency shall also extend its capacity to support the enhanced environmental risk assessments.

1.5.2. Added value of Union involvement (it may result from different factors, e.g. coordination gains, legal certainty, greater effectiveness or complementarities). For the purposes of this point 'added value of Union involvement' is the value resulting from Union intervention which is additional to the value that would have been otherwise created by Member States alone.

Reasons for action at European level (ex-ante): Ensuring access to medicines is a clear public health interest in the EU. The current level of harmonisation shows that the authorisation of medicines can be effectively regulated at EU level. Uncoordinated measures by Member States may result in distortions of competition and barriers to intra-Union trade for products that are relevant for the entire EU. The initiative respects national exclusive competence in health services and pricing and reimbursement of medicines.

Expected generated Union added value (ex-post)

Currently there is no Union intervention to increase patient access to newly authorised medicines, and there is a significant variation between Member States in terms of access, especially the smaller markets are disadvantaged. The Union intervention will rely on the combined EU market power in encouraging companies to serve all Member States and in a timely fashion.

Most authorised innovative medicines are authorised through the centralised procedure, at EU level. Therefore, enhancing regulatory support is not only more effective at EU-level than at Member State level but also probably the only feasible option.

A coordinated response at Union-level to monitoring and mitigating the risk of shortages can help to avoid actions such as uncoordinated stockpiling being taken and therefore have both a positive impact on public health and maintain the smooth functioning of the single market.

Environmental hazards know no borders, therefore only an EU-level coordinated and standardised mitigation of environmental risks stemming from pharmaceuticals manufacturing, use and disposal can be effective.

1.5.3. Lessons learned from similar experiences in the past

The EU pharmaceutical legislation roots back to 1961, the first common EU rules for authorisation. Much of the impetus behind the adoption of the legal framework stemmed from the determination to prevent a recurrence of the thalidomide disaster of the late 1950s, when thousands of babies were born with limb deformities as a result of their mothers taking a medicinal product during pregnancy. This experience, which shook public health authorities and the general public, made it clear that to safeguard public health, no medicinal product must ever again be marketed without prior authorisation.

Since then, a large body of legislation has been developed around this principle, with the progressive harmonisation of requirements for the granting of marketing authorisation, and post-marketing monitoring, implemented across the entire European Economic Area (EEA).

Beyond safety, and harmonised rules for medicinal products to enable a single market, incentives have been introduced to support innovation. Dedicated incentives for medicines for rare diseases and medicines for children have boosted research and innovation in these areas, leading to scientific breakthroughs and life-saving new products.

Both the obligations and incentives have proven to be largely effective, and the lessons learned from their application drove the current revision. Revision and modulation of existing obligations and incentives and adding new ones will serve new and recurring goals:

– Promoting innovation and addressing unmet medical needs
– Promoting access to affordable medicines
– Enhancing security of supply of medicines
– Reducing the environmental impact of medicines
– Reducing regulatory burden and providing a flexible and future-proof regulatory framework

1.5.4. Compatibility with the Multiannual Financial Framework and possible synergies with other appropriate instruments

The Agency should cooperate and promote synergies with other Union bodies, such as the European Centre for Disease and Control (ECDC), European Food Safety Authority (EFSA) and take full advantage and ensure consistency with the EU4Health programme and other EU programmes financing actions in the domain of public health.

1.5.5. Assessment of the different available financing options, including scope for redeployment

The overall budgetary impact of the revision to the Pharma legislation is 17.8 million EUR for the period 2024-2027 (excluding the costs for fee-financed staff). This amount will cover the development and the maintenance of the data register from Environmental Risk Assessment studies; activities related to shortage management and security of supply; the development of a new IT module for third-country inspections of decentralised manufacturing, development and maintenance of the union register of orphan designations and the support to “not-for-profit” entities. Most of these budgetary needs will be covered by EMA fees therefore the impact on the EU budget amounts to 4.4 million EUR. The 4.4 million EUR that will result in an increase of the EMA annual subsidy for the current MFF period will be redeployed internally within Heading 2b, by a corresponding reduction of the EU4Health programme’s budgetary envelope in years 2026 and 2027.

1.6. Duration and financial impact of the proposal/initiative

☐ **limited duration**

– ☐ in effect from [DD/MM]YYYY to [DD/MM]YYYY

– ☐ Financial impact from YYYY to YYYY for commitment appropriations and from YYYY to YYYY for payment appropriations.

☑ **unlimited duration**

– Implementation with a start-up period from 2023 to 2024,

– followed by full-scale operation.

1.7. Management mode(s) planned[3]

☑ **Direct management** by the Commission

– ☐ by its departments, including by its staff in the Union delegations;

– ☐ by the executive agencies

☐ **Shared management** with the Member States

☑ **Indirect management** by entrusting budget implementation tasks to:

– ☐ third countries or the bodies they have designated;

– ☐ international organisations and their agencies (to be specified);

– ☐ the EIB and the European Investment Fund;

– ☑ bodies referred to in Articles 70 and 71 of the Financial Regulation;

– ☐ public law bodies;

– ☐ bodies governed by private law with a public service mission to the extent that they provide adequate financial guarantees;

– ☐ bodies governed by the private law of a Member State that are entrusted with the implementation of a public-private partnership and that provide adequate financial guarantees;

[3] Details of management modes and references to the Financial Regulation may be found on the BudgWeb site: https://myintracomm.ec.europa.eu/budgweb/EN/man/budgmanag/Pages/budgmanag.aspx

– ☐ persons entrusted with the implementation of specific actions in the CFSP pursuant to Title V of the TEU, and identified in the relevant basic act.

– *If more than one management mode is indicated, please provide details in the 'Comments' section.*

Comments

2. MANAGEMENT MEASURES

2.1. Monitoring and reporting rules

Specify frequency and conditions.

All Union agencies work under a strict monitoring system involving an internal control coordinator, the Internal Audit Service of the Commission, the Management Board, the Commission, the Court of Auditors and the Budgetary Authority. This system is reflected and laid down in the EMA's founding regulation. In accordance with the Joint Statement on the EU decentralised agencies (the 'Common Approach'), the framework financial regulation (2019/715) and related Commission Communication C(2020)2297, the annual work programme and Single Programming Document of the Agency comprise detailed objectives and expected results, including a set of performance indicators. The Single Programming Document combines multiannual and annual programming as well as "strategy documents", e.g. on independence. DG SANTE comments through the Agency's Management Board and prepares a formal Commission Opinion on the Single Programming Document. The activities of the Agency will be measured against these indicators in the Consolidated Annual Activity Report.

The Agency will monitor periodically the performance of its internal control system to ensure that data is collected efficiently, effectively and timely and to identify internal control deficiencies, register and assess the results of controls, control deviations and exceptions. The results of the internal control assessments, including significant weaknesses identified and any differences as compared to internal and external audit findings will be disclosed in the Consolidated Annual Activity report.

2.2. Management and control system(s)

2.2.1. Justification of the management mode(s), the funding implementation mechanism(s), the payment modalities and the control strategy proposed

The annual EU subsidy will be transferred to the Agency in accordance with its payment needs and upon its request. The Agency will be subject to administrative controls including budgetary control, internal audit, annual reports by the European Court of Auditors, the annual discharge for the execution of the EU budget and possible investigations conducted by OLAF to ensure, in particular, that the resources allocated to the Agency are put to proper use. Through its representation in the Agency's Management Board and Audit Committee, the

Commission will receive audit reports and ensures that adequate actions are defined and timely implemented by the Agency to address the issues identified. All payments will remain pre-financing payments until the Agency's accounts have been audited by the European Court of Auditors and the Agency has submitted its final accounts. If necessary, the Commission will recover unspent amounts of the instalments paid to the Agency.

The activities of the Agency will also be subject to the supervision of the Ombudsman in accordance with Article 228 of the Treaty. These administrative controls provide a number of procedural safeguards to ensure that account is taken of the interests of the stakeholders.

2.2.2. Information concerning the risks identified and the internal control system(s) set up to mitigate them

The main risks relate to the Agency's performance and independence in implementing the tasks entrusted to it. Underperformance or impaired independence could hamper the achievement of the objectives of this initiative and also reflect negatively on the Commission's reputation.

The Commission and the Agency have put in place internal procedures that aim at covering the risks identified above. The internal procedures are in full compliance with the Financial Regulation and include anti-fraud measures and cost-benefit considerations.

First and foremost, sufficient resources should be made available to the Agency in both financial and staffing terms to achieve the objectives of this initiative.

Furthermore, quality management will include both the integrated quality-management activities and risk-management activities within the Agency. A risk review is conducted annually, with risks being assessed at a residual level, i.e. taking into account controls and mitigations already in place. Conducting self-assessments (as part of the EU Agencies benchmarking programme), annual reviews of sensitive functions and ex-post controls also fall within this area, as does maintain a register of exceptions.

To preserve impartiality and objectivity in every aspect of the Agency's work, a number of policies and rules on management of competing interests have been put in place and will be regularly updated, describing specific arrangements, requirements and processes applying to the Agency's Management Board, scientific committee members and experts, the Agency's staff and candidates, as well as consultants and contractors.

The Commission will be informed timely of relevant management and independence issues encountered by the Agency and will react upon notified issues timely and adequately.

2.2.3. Estimation and justification of the cost-effectiveness of the controls (ratio of "control costs ÷ value of the related funds managed"), and assessment of the expected levels of risk of error (at payment & at closure)

The Commission's and the Agency's internal control strategies take into consideration the main cost drivers, and the efforts already taken over several years to reduce the cost of controls, without compromising the effectiveness of controls. The existing control systems proved to be able to prevent and/or to detect errors and/or irregularities, and in case of errors or irregularities, to correct them.

In the past five years, the Commission's yearly costs of controls under indirect management represented less than 1% of the annual budget spent on subsidies paid to the Agency. The Agency allocated less than 0,5% of its total annual budget on control activities centering around integrated quality management, audit, anti-fraud measures, finance and verification processes, corporate risk management and self-assessment activities.

2.3. Measures to prevent fraud and irregularities

Specify existing or envisaged prevention and protection measures, e.g. from the Anti-Fraud Strategy.

As for its activities in indirect management, the Commission shall take appropriate measures ensuring that the financial interests of the European Union are protected by the application of preventive measures against fraud, corruption and any other illegal activities, by effective checks and, if irregularities are detected, by the recovery of the amounts wrongly paid and, where appropriate, by effective, proportional and deterrent penalties.

To this effect, the Commission adopted an anti-fraud strategy, latest update of April 2019 (COM(2019)176), covering preventive, detective and corrective measures.

The Commission or its representatives and the European Court of Auditors shall have the power of audit, on the basis of documents and on-the-spot, over all grant beneficiaries, contractors and subcontractors who have received Union funds. OLAF shall be authorised to carry out on-the-spot checks and inspections on economic operators concerned indirectly by such funding.

As regards the European Medicines Agency, the anti-fraud measures are provided for in Article 69 of Regulation (EC) No 726/2004 and the framework financial Regulation (2019/715). The Executive Director and the Management Board of the Agency will take the appropriate measures in accordance with the Internal Control Principles applied across all EU institutions. In line with the Common Approach and Article 42 of the framework financial Regulation, an anti-fraud strategy has been developed and is followed by the Agency.

The Agency's Anti-fraud strategy covers 3-year period and is accompanied by a corresponding action plan, outlining both specific focus areas and actions for the next years, and several continuous actions that are carried out every year, such as a specific standalone fraud risk assessment, with the identified fraud risks included in the overall Agency risk register. Anti-fraud trainings are organised as part of the induction training and via mandatory anti-fraud e-learning training for newcomers. Staff are made aware of how to report any suspects of wrongdoings and disciplinary procedures are in place as per the rules of the Staff Regulations.

3. ESTIMATED FINANCIAL IMPACT OF THE PROPOSAL/INITIATIVE

3.1. Heading(s) of the multiannual financial framework and expenditure budget line(s) affected

- Existing budget lines

In order of multiannual financial framework headings and budget lines.

Heading of multiannual financial framework	Budget line	Type of expenditure	Contribution			
	Number	Diff./Non-diff.[4]	from EFTA countries[5]	from candidate countries[6]	from third countries	within the meaning of Article 21(2)(b) of the Financial Regulation
2	06.100302 Special contribution for orphan medicinal products	Non-diff.	YES	NO	NO	NO

3.2. Estimated financial impact of the proposal/initiative

3.2.1. Summary of estimated impact on operational appropriations

– ☐The proposal/initiative does not require the use of operational appropriations

– ☑The proposal/initiative requires the use of operational appropriations, as explained below:

EUR million (to three decimal places)

Heading of multiannual financial framework	2	Cohesion, Resilience and Values

[4] Diff. = Differentiated appropriations / Non-diff. = Non-differentiated appropriations.
[5] EFTA: European Free Trade Association.
[6] Candidate countries and, where applicable, potential candidates.

DG: SANTE			Year **2024**	Year **2025**	Year **2026**	Year **2027 and subsequent years**	**TOTAL**[7]
• Operational appropriations							
06.100302 Special contribution for orphan medicinal products	Commitments	(1b)			1.172	3.196	4.368
	Payments	(2b)			1.172	3.196	4.368
Appropriations of an administrative nature financed from the envelope of specific programmes[8]							
Budget line		(3)					
TOTAL appropriations for DG SANTE	Commitments	=1a+1b +3			1.172	3.196	4.368
	Payments	=2a+2b +3			1.172	3.196	4.368

• TOTAL operational appropriations	Commitments	(4)			1.172	3.196	4.368
	Payments	(5)			1.172	3.196	4.368
• TOTAL appropriations of an administrative nature financed from the envelope for specific programmes		(6)					
TOTAL appropriations under HEADING <2b> of the multiannual financial framework	Commitments	=4+ 6			1.172	3.196	4.368
	Payments	=5+ 6			1.172	3.196	4.368

7 For 2026 the total amount covers the costs for 6 TAs. For 2027 the total amount covers the costs for 6 TAs (1.196 million EUR) and the costs for the incentives to "not-for-profit" entities (2 million EUR).

8 Technical and/or administrative assistance and expenditure in support of the implementation of EU programmes and/or actions (former 'BA' lines), indirect research, direct research.

Heading of multiannual financial framework	7	'Administrative expenditure'

This section should be filled in using the 'budget data of an administrative nature' to be firstly introduced in the Annex to the Legislative Financial Statement (Annex V to the internal rules), which is uploaded to DECIDE for interservice consultation purposes.

EUR million (to three decimal places)

		Year **2024**	Year **2025**	Year **2026**	Year **2027 and subsequent years**	Enter as many years as necessary to show the duration of the impact (see point 1.6)			**TOTAL**
DG: SANTE									
• Human resources									
• Other administrative expenditure									
TOTAL DG <…….>	Appropriations								

TOTAL appropriations under HEADING 7 of the multiannual financial framework	(Total commitments = Total payments)								

EUR million (to three decimal places)

		Year **2024**	Year **2025**	Year **2026**	Year **2027**	Enter as many years as necessary to show the duration of the impact (see point 1.6)			**TOTAL**
TOTAL appropriations under HEADINGS 1 to 7 of the multiannual financial framework	Commitments			1.172	3.196				4.368
	Payments			1.172	3.196				4.368

3.2.2. *Estimated output funded with operational appropriations*

Commitment appropriations in EUR million (to three decimal places)

Indicate objectives and outputs ⇩			Year **2024**		Year **2025**		Year **2026**		Year **2027 and subsequent years**		**TOTAL**	
	OUTPUTS											
	Type[9]	Average cost	No	Cost	No	Cost	No	Cost	No	Cost	Total No	Total cost
Specific objective 1. Promote innovation, in particular for unmet medical needs, including for rare disease patients and children.												
Support to "not-for-profit" entities								1.172		3.196		4.368
Subtotal for specific objective No 1								1.172		3.196		4.368
TOTALS								1.172		3.196		4.368
- Output												

[9] Outputs are products and services to be supplied (e.g.: number of student exchanges financed, number of km of roads built, etc.).

3.2.3. Estimated impact on EMA's human resources

– ☐ The proposal/initiative does not require the use of appropriations of an administrative nature

– ☐ The proposal/initiative requires the use of appropriations of an administrative nature, as explained below:

EUR million (to three decimal places)

	Year **2024**	Year **2025**	Year **2026**	Year **2027 and subsequent years**	**TOTAL**
Temporary agents (AD Grades)			0.781	0.797	1.578
Temporary agents (AST grades)			0.391	0.399	0.790
Contract staff					
Seconded National Experts					
TOTAL			**1.172**	**1.196**	**2.368**

Staff requirements (FTE): Total posts Union funded and funded from fees

	Year **2024**	Year **2025**	Year **2026**	Year **2027 and subsequent years**	**TOTAL**
Temporary agents (AD Grades)	13	22	33	40	40
Temporary agents (AST grades)	6	15	19	20	20
Contract staff					
Seconded National Experts					

TOTAL	**19**	**37**	**52**	**60**	**60**

The appropriations required for human resources and other expenditure of an administrative nature will be met by appropriations from the DG that are already assigned to management of the action and/or have been redeployed within the DG, together if necessary with any additional allocation which may be granted to the managing DG under the annual allocation procedure and in the light of budgetary constraints.

3.2.3.1. Estimated requirements of human resources

– ☐ The proposal/initiative does not require the use of human resources.

– ☐ The proposal/initiative requires the use of human resources, as explained below:

Estimate to be expressed in full time equivalent units

		Year **2024**	Year **2025**	Year **2026**	Year **N+3**	Enter as many years as necessary to show the duration of the impact (see point 1.6)		
• Establishment plan posts (officials and temporary staff)								
20 01 02 01 (Headquarters and Commission's Representation Offices)								
20 01 02 03 (Delegations)								
01 01 01 01 (Indirect research)								
01 01 01 11 (Direct research)								
Other budget lines (specify)								
• External staff (in Full Time Equivalent unit: FTE)[103]								
20 02 01 (AC, END, INT from the 'global envelope')								
20 02 03 (AC, AL, END, INT and JPD in the delegations)								
XX 01 xx **yy zz** [104]	- at Headquarters							
	- in Delegations							
01 01 01 02 (AC, END, INT - Indirect research)								
01 01 01 12 (AC, END, INT - Direct research)								
Other budget lines (specify)								
TOTAL								

XX is the policy area or budget title concerned.

The human resources required will be met by staff from the DG who are already assigned to management of the action and/or have been redeployed within the DG, together if necessary with any additional allocation which may be granted to the managing DG under the annual allocation procedure and in the light of budgetary constraints.

Description of tasks to be carried out from the FTE, funded by Union contribution:

Officials and temporary staff	The requested FTE (4 AD and 2 AST) are necessary to set up the Academia Office at EMA that will be managing the procedures. The tasks of the office will be similar to the tasks of the SME office and will include procedural and administrative assistance to "not-for-profit" entities, including direct assistance and briefing meetings on regulatory strategy, providing fee waivers and reductions to eligible entities, provide free-of-charge translations of the product information in all EU languages for initial EU marketing authorisations, provide training and education to "not-for-profit" entities, etc
External staff	

103 AC= Contract Staff; AL = Local Staff; END= Seconded National Expert; INT = agency staff; JPD= Junior Professionals in Delegations.

104 Sub-ceiling for external staff covered by operational appropriations (former 'BA' lines).

3.2.4. Description of tasks to be carried out from the FTE, funded by EMA fees:

Officials and temporary staff	The requested staff (54 FTE) will be: • managing (AD profiles) and providing support (AST profiles) to operational expert groups in the area of the Environmental Risk Assessment (ERA); • with a scientific and regulatory profile to work in the shortages management and security of supply; • Good Manufacturing Practice and Good Clinical Practice inspectors (AD) necessary to establish an EU inspectorate resourced by EMA staff that would provide help to the inspections done by Member States (lacking resources), and deal with emergency situations which require dedicated and dependable intervention (e.g., similar to inspections required during the pandemic); • Legal officers (AD profiles), needed in the field of orphan designations that are already today a litigious topic and so it is assumed the proposed changes in the decision making on orphan designation would generate an increased in workload for even more legal queries and litigations; • defining business requirements for the data register, following up on the implementation and perform the related scientific activities when the register is live;, develop trainings on ERA, etc.; • providing administrative support to the operational expert groups; • working in the area of inspection planning; • general assistants, assistants, supporting on procedural aspects or working on document creation.
External staff	

3.2.5. Compatibility with the current multiannual financial framework

The proposal/initiative:

– ☑ can be fully financed through redeployment within the relevant heading of the Multiannual Financial Framework (MFF).

The increase of appropriations for EMA budget line 06.100302 in years 2026 and 2027 by 4.4 million EUR, will be done via internal redeployment within heading 2b, i.e. by an equal reduction of the EU4Health budget line 06.0601 for this period.

– ☐ requires use of the unallocated margin under the relevant heading of the MFF and/or use of the special instruments as defined in the MFF Regulation.

Explain what is required, specifying the headings and budget lines concerned, the corresponding amounts, and the instruments proposed to be used.

– ☐ requires a revision of the MFF.

Explain what is required, specifying the headings and budget lines concerned and the corresponding amounts.

3.2.6. Third-party contributions

The proposal/initiative:

– ☑ does not provide for co-financing by third parties

– ☐ provides for the co-financing by third parties estimated below:

Appropriations in EUR million (to three decimal places)

	Year **2024**	Year **2025**	Year **2026**	Year **2027 and subsequent years**	Enter as many years as necessary to show the duration of the impact (see point 1.6)			Total
Specify the co-financing body								
TOTAL appropriations co-financed								

3.3. Estimated impact on revenue

– ☑ The proposal/initiative has no financial impact on revenue.

– ☐ The proposal/initiative has the following financial impact:

  – ☐ on own resources

  – ☐ on other revenue

  – please indicate, if the revenue is assigned to expenditure lines ☐

EUR million (to three decimal places)

Budget revenue line:	Appropriations available for the current financial year	Impact of the proposal/initiative[105]						
		Year **2024**	Year **2025**	Year **2026**	Year **2027 and subsequent years**	Enter as many years as necessary to show the duration of the impact (see point 1.6)		
Article …….								

For assigned revenue, specify the budget expenditure line(s) affected.

Other remarks (e.g. method/formula used for calculating the impact on revenue or any other information).

[105] As regards traditional own resources (customs duties, sugar levies), the amounts indicated must be net amounts, i.e. gross amounts after deduction of 20 % for collection costs.