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Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

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

(Text with EEA relevance)

{SEC(2023) 390 final} - {SWD(2023) 191 final} - {SWD(2023) 192 final} - {SWD(2023) 193 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 medicinal 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 reform of the legislation alone. Despite this, EU pharmaceutical legislation can be an enabling and connecting factor for innovation, access, affordability and environmental protection.

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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).

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 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 (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

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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).

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).

requirements, which are currently laid down in separate legislative acts, should be integrated into the regulation and this directive in order to ensure clarity and coherence of all the measures applicable to these medicinal 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.

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

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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).

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).

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, the 'HTA Regulation')[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 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].

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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).

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.

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.

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.

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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).

- **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 directive introduces a large number of amendments to Directive 2001/83/EC and incorporates part of the current provisions and amendments to Regulation (EC) No 1901/2006. A new directive repealing Directive 2001/83/EC (rather than an amending directive) is therefore considered the appropriate legal instrument. A directive remains the best choice of legal instrument to avoid fragmentation of national legislation on medicinal products for human use, given that the legislation is based on a system of national and EU marketing authorisations. National authorisations are granted and managed on the basis of national laws implementing the EU law. The evaluation of the general pharmaceutical legislation has not found that the choice of legal instrument has caused specific problems or reduced the level of harmonisation. In addition, a REFIT Platform opinion[30] from 2019 showed that there was no support among the Member States to turn Directive 2001/83/EC into a regulation.

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 'back-to-back' evaluations and impact assessments of the general pharmaceutical legislation and of the Orphan and Paediatric Regulations[31].

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[32].

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.

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30 The EU's efforts to simplify legislation – 2019 Annual Burden survey, https://commission.europa.eu/system/files/2020-08/annual_burden_survey_2019_4_digital.pdf.

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

32 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.

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[33].

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 lifecycle 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 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.

[33] ICH – harmonisation for better health, https://www.ich.org/.

- **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[34]. 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.

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

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 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 reform.

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 against 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[35] 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 two 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.

[35] Commission staff working document, Impact Assessment.

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.

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 revision 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 15% increased access, meaning 67 million more people residing in the EU who can potentially benefit from a new medicinal product, and more medicinal products addressing unmet medical needs at the same cost for the public payers as today. 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 originator companies would have additional costs and benefits from the incentives and the market launch conditionality, and overall they would see an increase in their sales. Some increased costs will be associated with the reporting on shortages. 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 revision 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 one

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 an additional one or two 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 six 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 one 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 (+one 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 six 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 lifecycle 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 pharmaceutical industry.

- 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 financial impact is shown in the Legal Financial Statement attached to the 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.

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[36] 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 the deadline for its transposition.

- **Explanatory documents (for directives)**

Following the ruling of the European Court of Justice in Commission vs Belgium (Case C-543/17), Member States must accompany their notifications of national transposition measures with sufficiently clear and precise information, indicating which provisions of national law transpose which provisions of a directive. This must be provided for each obligation, not only at article level. If Member States comply with this obligation, they would not need, in principle, to send explanatory documents on the transposition to the Commission.

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

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

The proposed revision of the pharmaceutical legislation consists of a proposal for a new directive and a proposal for a new regulation (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. While procedural requirements applicable to paediatric medicinal products are primarily integrated in the new regulation, the general framework for the authorisation and rewarding of these products have been included in the new directive. The main areas of the revision under the proposed new regulation are covered by the explanatory memorandum of the accompanying proposal for a regulation.

Annex II to the directive contains the existing text of Annex I. Annex II will be updated by delegated act. The delegated act will be adopted and applied before the deadline for the transposition of the directive.

The proposed directive includes the following main areas of revision:

Promoting innovation and access to affordable medicinal products - creating a balanced pharmaceutical ecosystem

To enable innovation and promote the competitiveness of the EU pharmaceutical industry, in particular SMEs, the provisions of the proposed directive work in synergy with those of the proposed regulation. In this respect, a balanced system of incentives is proposed. The system rewards innovation, especially in areas of unmet medical needs, and innovation reaches patients and improves access across the EU. 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 also measures under 'Reducing regulatory burden and providing a flexible regulatory framework to support innovation and competitiveness' below and in the proposed regulation).

Introduction of variable incentives related to regulatory data protection and rewarding of innovation in areas of unmet medical needs

The current standard period of regulatory data protection will be reduced from eight years to six years. Nevertheless, this remains competitive given what other regions offer. Furthermore, marketing authorisation holders will benefit from additional periods of data protection (beyond the standard six years) if they launch the medicinal products in all Member States covered by the marketing authorisation (+two years), if they address unmet medical needs (+six months), if they conduct comparative clinical trials (+six months) or for an additional therapeutic indication (+ one year).

Prolongation of data protection for the market launch will be granted if the medicinal product is supplied in accordance with the needs of the Member States concerned within two years from the marketing authorisation (or within three years in the case of SMEs, not-for-profit entities or companies with limited experience in the EU system). Member States have the possibility to waive the condition of launch in their territory for the purpose of the prolongation. This is expected to be the case particularly in situations where launch in a particular Member State is materially impossible or because there are special reasons why a Member State wishes that launch takes place later. Such a waiver does not mean that a Member State is not interested in the medicinal product altogether.

Prolongation of data protection for addressing unmet medical need will be granted if the medicinal product is for a life-threatening or seriously debilitating disease with remaining high morbidity or mortality, and the use of the medicinal product results in a meaningful reduction in disease morbidity or mortality. The various elements of this criterion-based definition of unmet medical need (e.g. "remaining high morbidity or mortality") will be further specified in implementing acts, taking into account scientific input by the EMA, to ensure that the concept of unmet medical need reflects scientific and technological developments and current knowledge in underserved diseases.

The period of regulatory data protection is followed by a period of market protection (two years), which remains unchanged under the proposed directive as compared to the existing rules.

With the additional conditional protection periods, the period of regulatory protection (data and market protection) can add up to 12 years for innovative medicines (if a new therapeutic indication is added after the initial marketing authorisation).

In addition, for a medicinal product addressing an unmet medical need, a company will benefit from an enhanced scientific and regulatory support scheme ('PRIME') and from accelerated assessment mechanisms. The PRIME support scheme will boost innovation in areas of unmet medical needs, allow pharmaceutical companies to speed up the development process and allow earlier patient access. The various elements of this criterion-based definition of unmet medical need (e.g "remaining high morbidity or mortality") will be further specified in implementing acts, taking into account scientific input by the EMA, to ensure that the concept of unmet medical need reflects scientific and technological developments and current knowledge in underserved diseases.

Increased competition from earlier market entry of generic and biosimilar medicinal products

The 'Bolar exemption' (under which studies can be carried out for subsequent regulatory approval of generics and biosimilars during the patent or supplementary protection certificate protection of the reference medicinal product), will be broadened in scope and its harmonised application in all Member States ensured. In addition, procedures for the authorisation of generics and biosimilars will be simplified: as a general rule, risk management plans will no longer be required for generic and biosimilar medicinal products, considering that the reference medicinal product already has such a plan.

The interchangeability of biosimilars with their reference medicinal products is also better recognised based on accumulated scientific experience with such medicinal products. In addition, the act provides an incentive for repurposing off-patent, added value medicinal products. This supports innovation, resulting in a new therapeutic indication that offers significant clinical benefit in comparison with existing therapies. Taken together, these measures will facilitate earlier market entry of generics and biosimilars, thus increasing competition and contributing to the objectives of promoting affordability of medicinal products and patient access.

Increased transparency on the contribution of public funding to research & development costs

Marketing authorisation holders will be required to publish a report listing all direct financial support received from any public authority or publicly funded body for the research and development of the medicinal product, whether successful or not successful. Such information will be easily accessible to the public on a dedicated webpage of the marketing authorisation holder and in the database of all medicinal products for human use authorised in the EU. Greater transparency around public funding for medicinal products development is expected to help maintain or improve access to affordable medicinal products.

Reducing the environmental impact of medicinal products

Strengthening the requirements for the environmental risk assessment (ERA) in the market authorisation of medicinal products will drive pharmaceutical companies to evaluate and limit potential adverse effects to the environment and public health. The scope of the ERA is extended to cover new protection goals such as the risks of antimicrobial resistance.

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

Reduction of the regulatory burden will be ensured by measures simplifying regulatory procedures and improving digitisation. These include provisions on electronic submission of applications and electronic product information (ePI) on authorised medicinal products, the latter being an option that Member States can opt for based on their particular readiness to replace the paper leaflet. Measures to reduce regulatory burden also include abolishing the renewal and the sunset clause. The reduction of administrative burden through simplification and digitisation measures will benefit in particular to SMEs and not-for-profit entities involved in developing medicinal products. The various measures to reduce the regulatory burden will strengthen the competitiveness of the pharmaceutical sector.

Adapted frameworks with specific regulatory requirements tailored to the characteristics or methods inherent to certain, especially novel, medicinal products will ensure an agile and future-proof regulatory environment while keeping the existing high standards of quality, safety and efficacy. Such adapted frameworks could draw on the results of the regulatory sandboxes established in the proposed regulation.

The proposed directive provides rules for products which combine a medicinal product and a medical device and specifies the interplay with the medical devices legal framework. These provisions improve legal certainty in order to accommodate increasing innovation in this field. In addition, the interplay with the legislation on substances of human origin ('SoHO' as defined in the 'SoHO Regulation') is further clarified with a new definition of 'SoHO-derived medicinal product' and the possibility for the EMA to make a scientific recommendation on a medicinal product's regulatory status, under the classification mechanism proposed in the regulation, in consultation with the relevant SoHO regulatory body. The proposed directive also introduces measures to improve the application of hospital exemptions for advanced therapy medicinal products.

Specific provisions for new platform technologies[37] will facilitate the development and authorisation of such types of innovation for the benefit of patients.

Specific measures related to quality and manufacturing

The advent of new therapeutic approaches that have features such as very short shelf-lives, and which may be highly personalised, enable decentralised manufacture and use of patient-specific medicinal products. These paradigms of decentralised or personalised manufacturing require a shift away from existing regulatory frameworks that are designed to meet the regulatory expectations for large-scale centralised manufacture. The new legal framework incorporates a risk-based and flexible approach that will enable the manufacture or testing of a wide range of medicinal products in close proximity to the patient.

[37] When a certain process/method is used to manufacture specific individualised treatments, i.e. adjustments to the medicine are made based on the characteristics of the patient or the causing pathogen.

2023/0132 (COD)

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

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

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

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

Having regard to the opinion of the Committee of the Regions,

Acting in accordance with the ordinary legislative procedure,

Whereas:

(1) The Union general pharmaceutical legislation was established in 1965 with the dual objective of safeguarding public health and harmonising the internal market for medicines. It has developed considerably since then, but these overarching objectives have guided all revisions. The legislation governs the granting of marketing authorisations for all medicines for human use by defining conditions and procedures to enter and remain on the market. A fundamental principle is that a marketing authorisation is granted only to medicines with a positive benefit-risk balance after assessment of their quality, safety and efficacy.

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

(3) This revision is part of the implementation of the Pharmaceutical strategy for Europe and aims to promote innovation, in particular for unmet medical needs, while reducing regulatory burden and the environmental impact of medicines; ensure access to innovative and established medicines for patients, with special attention to enhancing security of supply and addressing risks of shortages, taking into account the challenges of the smaller markets of the Union; and create a balanced and competitive system that keeps medicines affordable for health systems while rewarding innovation.

(4) This revision focuses on provisions relevant to achieve its specific objectives; therefore it covers all but provisions concerning falsified medicines, homeopathic and traditional herbal medicines. Nevertheless, for the sake of clarity, it is necessary to replace Directive 2001/83/EC of the European Parliament and of the Council[1] with a new Directive. The provisions on falsified medicines, homeopathic medicines and traditional herbal medicines are therefore maintained in this Directive without changing their substance compared to previous harmonisations. However, in view of the changes in the governance of the Agency, the Herbal Committee is replaced by a working group.

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

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

(7) The EU and all its Member States as parties to the United Nations Convention on the Rights of Persons with Disabilities are bound by its provisions to the extent of their competences. This includes the right to access information as set out in Article 21 and the right to the enjoyment of the highest attainable standard of health without discrimination on the basis of disability as set in Article 25.

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

[1] 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).

(9) Medicinal products for rare diseases and for children, should be subject to the same conditions as any other medicinal product concerning their quality, safety and efficacy, for example for what concerns the marketing authorisation procedures, quality and the pharmacovigilance requirements. However, specific requirements also apply to them considering their unique characteristics. Such requirements, which are currently defined in separate legislations, should be integrated in general pharmaceutical legal framework in order to ensure clarity and coherency of all the measures applicable to these medicinal products. Furthermore, as some medicinal products authorised for use in children are authorised by the Member States, specific provisions should be integrated in this Directive.

(10) The system of a directive and regulation for the general pharmaceutical legislation should be maintained to avoid fragmentation of national legislation on medicinal products for human use, given that the legislation is based on a system of national Member States and Union marketing authorisations. Member States national marketing authorisations are granted and managed on the basis of national law implementing the Union pharmaceutical law. The evaluation of the general pharmaceutical legislation has not shown that the choice of legal instrument has caused specific problems or created disharmonisation. In addition, a REFIT Platform[2] opinion in 2019 showed that there was not support among the Member States to turn Directive 2001/83/EC into a Regulation.

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

(12) The definitions and scope of Directive 2001/83/EC should be clarified in order to achieve high standards for the quality, safety and efficacy of medicinal products and to address potential regulatory gaps, without changing the overall scope, due to scientific and technological developments, e.g. low-volume products, bedside-manufacturing or personalised medicinal products that do not involve an industrial manufacturing process.

(13) To avoid the duplication of requirements for medicinal products in this Directive and in the Regulation, the general standards in regards to quality, safety and efficacy of medicinal products laid down in this Directive shall be applicable to medicinal products covered by national marketing authorisation and also to medicinal products covered by centralised marketing authorisation. Therefore, the requirements for an application for medicinal product are valid for both, also the rules on prescription status, product information, regulatory protection and rules on manufacturing, supply, advertising, supervision and other national requirements shall be applicable to medicinal products covered by centralised marketing authorisation.

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

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[2] The EU's efforts to simplify legislation – 2019 Annual Burden survey, https://commission.europa.eu/system/files/2020-08/annual_burden_survey_2019_4_digital.pdf.

(15) In order to take account both of the emergence of new therapies and of the growing number of so-called ‘borderline’ products between the medicinal product sector and other sectors, certain definitions and derogations should be modified, so as to avoid any doubt as to the applicable legislation. With the same objective of clarifying situations when a product fully falls within the definition of a medicinal product and also meet the definition of other regulated products, the rules for medicinal products under this Directive apply. Furthermore, to ensure the clarity of applicable rules, it is also appropriate to improve the consistency of the terminology of the pharmaceutical legislation and clearly indicate the products excluded from the scope of this Directive.

(16) The new definition for a substance of human origin (SOHO) by the [SoHO Regulation] covers any substance collected from the human body in whatever manner, whether it contains cells or not and regardless of whether it meets the definition of 'blood', 'tissue' or 'cell', for example human breast milk, intestinal microbiota and any other SoHO that may be applied to humans in the future. Such substances of human origin, other than tissues and cells, may become SoHO derived medicinal products, other than ATMPs, when the SoHO is subject to an industrial process involving systematisation, reproducibility and operations performed on a routine basis or batch-wise resulting in a product of standardised consistency. When a process concerns extraction of an active ingredient from the SoHO, other than tissues and cells, or a transformation of a SoHO, other than tissues and cells, by changing its inherent properties, this should also be considered a SoHO derived medicinal product. When a process concerns concentrating, separating or isolating elements in the preparation of blood components, this should not be considered as changing their inherent properties.

(17) For avoidance of doubt, the safety and quality of human organs intended for transplantation are regulated only by Directive 2010/53/EU of the European Parliament and of the Council[3], and the safety and quality of substances of human origin intended for medically assisted reproduction are regulated only by [SoHO Regulation or if not in force, Directive 2004/23/EC].

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

[3] Directive 2010/45/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).

(19) This Directive should be without prejudice to the provisions of Council Directive 2013/59/Euratom[4], including with respect to justification and optimisation of protection of patients and other individuals subject to medical exposure to ionising radiation. In the case of radiopharmaceuticals used for therapy, marketing authorisations, posology and administration rules have to notably respect that Directive's requirements that exposures of target volumes are to be individually planned, and their delivery appropriately verified taking into account that doses to non-target volumes and tissues are to be as low as reasonably achievable and consistent with the intended therapeutic purpose of the exposure.

(20) In the interest of public health, a medicinal product should only be allowed to be placed on the market in the Union when the marketing authorisation has been granted to the medicinal product, and its quality, safety and efficacy have been demonstrated. However, exemption should be provided from this requirement in situations characterised by an urgent need to administer a medicinal product to address the specific needs of a patient, or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation that could cause harm. In particular, to fulfil special needs, Member States should be allowed to exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under their direct personal responsibility. Member States should be also allowed to temporarily authorise the distribution of an unauthorised medicinal product in response to a suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.

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

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

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

(24) It is therefore necessary to introduce a requirement for new medicinal products or when developing paediatric indications of already authorised products covered by a patent or a supplementary protection certificate to present either the results of studies in the paediatric population in accordance with an agreed paediatric investigation plan or proof of having

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

obtained a waiver or deferral, at the time of filing a marketing authorisation application or an application for a new therapeutic indication, new pharmaceutical form or new route of administration.

However, in order to avoid exposing children to unnecessary clinical trials or due to the nature of the medicinal products, that requirement should not apply to generics or similar biological medicinal products and medicinal products authorised through the well-established medicinal use procedure, nor to homeopathic medicinal products and traditional herbal medicinal products authorised through the simplified registration procedures of this Directive.

(25) In order to ensure that the data supporting the marketing authorisation concerning the use of a product in children to be authorised under this regulation have been correctly developed, the competent authorities should check compliance with the agreed paediatric investigation plan and any waivers and deferrals at the validation step for marketing authorisation applications.

(26) In order to reward the compliance with all the measures included in the agreed paediatric investigation plan, for products covered by a supplementary protection certificate, if relevant information on the results of the studies conducted is included in the product information, a reward should be granted in the form of a six month extension of the supplementary protection certificate created by [Regulation (EC) No 469/2009 of the European Parliament and of the Council[5]- OP please replace reference by new instrument when adopted].

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

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

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

[5] Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (OJ L 152, 16.6.2009, p. 10).

product, the results of the appropriate non-clinical tests or clinical studies shall be provided to the extent necessary to establish a scientific bridge to the data relied upon in the marketing authorisation for the reference medicinal product.

The same applies to bio-hybrids i.e. in cases where a biosimilar medicinal product has changes in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference biological medicinal product. In the latter two situations, the scientific bridge establishes that the active substance of the hybrid does not differ significantly in properties with regard to safety or efficacy. Where it differs significantly in respect of those properties, the applicant needs to submit a full application.

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

(31) Directive 2010/63/EU of the European Parliament and of the Council[6] lays down provisions on the protection of animals used for scientific purposes based on the principles of replacement, reduction and refinement. Any study involving the use of animals, which provides essential information on the quality, safety and efficacy of a medicinal product, should take into account those principles of replacement, reduction and refinement, where they concern the care and use of live animals for scientific purposes, and should be optimised in order to provide the most satisfactory results whilst using the minimum number of animals. The procedures of such testing should be designed to avoid causing pain, suffering, distress or lasting harm to animals and should follow the available EMA and ICH guidelines. In particular, the marketing authorisation applicant and the marketing authorisation holder should take into account the principles laid down in Directive 2010/63/EU, including, where possible, use new approach methodologies in place of animal testing. These can include but are not limited to: in vitro models, such as microphysiological systems including organ-on-chips, (2D and 3D-) cell culture models, organoids and human stem cells-based models; in silico tools or read-across models.

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

(33) With respect to clinical trials, in particular those conducted outside the Union, on medicinal products destined to be authorised within the Union, it should be verified, at the time of the evaluation of the marketing authorisation application, that these trials were conducted in accordance with the principles of good clinical practice and the ethical requirements equivalent to the provisions of Regulation (EU) 536/2014 of the European Parliament and of the Council[7].

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[6] 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).

[7] 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).

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

(35) With the exception of those medicinal products that are subject to the centralised authorisation procedure established by [revised Regulation (EU) No. 726/2004], a marketing authorisation for a medicinal product should be granted by a competent authority in one Member State. In order to avoid unnecessary administrative and financial burdens for applicants and competent authorities, a full in-depth assessment of an application for the authorisation of a medicinal product should be carried out only once. It is appropriate therefore to lay down special procedures for the mutual recognition of national authorisations. Moreover, it should be possible to submit the same application in parallel in several Member States for the purpose of a common assessment under the lead of one of the Member States concerned.

(36) Moreover, rules should be established under those procedures to resolve any disagreements between competent authorities in a coordination group for mutual recognition and decentralised procedures medicinal products (‘the coordination group’) without undue delay. In the event of a disagreement between Member States about the quality, the safety or the efficacy of a medicinal product, a scientific evaluation of the matter should be undertaken according to a Union standard, leading to a single decision on the area of disagreement binding on the Member States concerned. Whereas this decision should be adopted by a rapid procedure ensuring close cooperation between the Commission and the Member States.

(37) In certain cases of major disagreement that cannot be solved, the case should be escalated and be subject to a scientific opinion of the Agency, which is then implemented through a Commission Decision.

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

(39) In the interest of as broad as possible access to medicinal products, a Member State that has an interest in receiving access to a particular medicinal product undergoing authorisation

through the decentralised and mutual recognition procedures should be able to opt-into that procedure

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

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

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

(43) Member States should ensure adequate funding of competent authorities to carry out their tasks under this Directive and [revised Regulation (EU) 726/2004]. In addition, Member States should ensure adequate resources are assigned by the competent authorities for the purpose of their contributions to the work of the Agency, taking into account the cost-based remuneration they receive from the Agency.

(44) As regards access to medicinal products, previous amendments to the Union pharmaceutical legislation have addressed this issue by providing for accelerated assessment of marketing authorisation applications or by allowing conditional marketing authorisation for medicinal products for unmet medical need. While these measures accelerated the authorisation of innovative and promising therapies, these medicinal products do not always reach the patient and patients in the Union still have different levels of access to medicinal products. Patient access to medicinal products depends on many factors. Marketing authorisation holders are not obliged to market a medicinal product in all Member States; they may decide not to market their medicinal products in, or withdraw them from, one or more Member States. National pricing and reimbursement policies, the size of the population, the organisation of health systems and national administrative procedures are other factors influencing market launch and patient access.

(45) Addressing unequal patient access and affordability of medicinal products has become a key priority of the Pharmaceutical Strategy for Europe, as also highlighted by Council conclusions[8] and a resolution of the European Parliament[9]. Member States called for revised mechanisms and incentives for development of medicinal products tailored to the level of unmet medical need, while ensuring health system sustainability, patient access and availability of affordable medicinal products in all Member States.

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

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

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

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

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

(49) Joint procurement, whether within a country or across countries, can improve access, affordability, and security of supply of medicines, in particular for smaller countries. Member States interested in joint procurement of medicines can make use of Directive 2014/24/EU[10], which sets out purchasing procedures for public buyers, the Joint Procurement Agreement[11] and the proposed revised Financial Regulation[12]. Upon request from the Member States the Commission may support interested Member States by facilitating coordination to enable access to medicines for patients in the Union as well as information exchange, in particular for medicines for rare and chronic diseases.

(50) The establishment of a criteria-based definition of 'unmet medical need' is required to incentivise the development of medicinal products in therapeutic areas that are currently underserved. To ensure that the concept of unmet medical need reflects scientific and technological developments and current knowledge in underserved diseases, the Commission should specify and update using implementing acts, the criteria of satisfactory method of diagnosis, prevention or treatment, 'remaining high morbidity or mortality', 'relevant patient population' following scientific assessment by the Agency. The Agency will seek input from a broad range of authorities or bodies active along the lifecycle of medicinal products in the framework of the consultation process established under the [revised Regulation (EC) No 726/2004] and also take into account scientific initiatives at EU level or between Member States related to analysing unmet medical needs, burden of disease and priority setting for research and development. The criteria for 'unmet medical need' can be subsequently used by Member States to identify specific therapeutic areas of interest.

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

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

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

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

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[10] Directive 2014/24/EU of the European Parliament and of the Council of 26 February 2014 on public procurement and repealing Directive 2004/18/EC (OJ L 94, 28.3.2014, p. 65).

[11] 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.

[12] COM/2022/223 final.

(55) When applying the provisions on market launch incentives, marketing authorisation holders and Member States should do their utmost to achieve a mutually agreed supply of medicinal products in accordance with the needs of the Member State concerned, without unduly delaying or hindering the other party from enjoying its rights under this Directive.

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

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

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

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

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

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

(62) The suspension of the regulatory data protection should be granted only for the duration of the compulsory licence. A ‘suspension‘ of data and market protection in cases of public health emergency shall mean that data and market protection shall produce no effect in

relation to the particular licensee of the compulsory licence while that compulsory licence is in effect. When the compulsory licence ends, the data and market protection shall resume their effect. The suspension should not result in an extension of the original duration.

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

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

(65) The competent authorities should refuse the validation for an application for a marketing authorisation referring to data of a reference medicinal product only on the basis of the grounds set out in this Directive. The same applies to any decision to grant, vary, suspend, restrict or revoke the marketing authorisation. The competent authorities cannot base their decision on any other grounds. In particular, those decisions cannot be based on the patent or SPC status of the reference medicinal product.

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

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

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

(69) The pollution of waters and soils with pharmaceutical residues is an emerging environmental problem, and there is scientific evidence that the presence of those substances in the environment from their manufacturing, use and disposal poses a risk to the environment and public health. The evaluation of the legislation showed that strengthening of existing measures to reduce the impact of medicinal products' lifecycle on the environment and public health is required. Measures under this Regulation complement the main environmental legislation, in particular the Water Framework Directive (2000/60/EC[13]), the Environmental Quality Standard Directive (2008/105/EC[14]) the Groundwater Directive (2006/118/EC[15]), the Urban Wastewater Treatment Directive (91/271/EEC[16]), the Drinking Water Directive (2020/2184[17]) and the Industrial Emissions Directive (2010/75/EU[18]).

(70) Marketing authorisation applications for medicinal products in the Union should include an Environmental Risk Assessment (ERA) and risk mitigation measures. If the applicant fails to submit a complete or sufficiently substantiated environmental risk assessment or they do not propose risk mitigation measures to sufficiently address the risks identified in the environmental risk assessment, the marketing authorisation should be refused. The ERA should be updated when new data or knowledge about relevant risks become available.

(71) Marketing authorisation applicants should take into account environmental risk assessment procedures of other EU legal frameworks that may apply to chemicals dependent on their use. Further to this Regulation, there are four main other frameworks: (i) Industrial chemicals (REACH, (Regulation (EC) No 1907/2006); (ii) Biocides (Regulation (EC) No 528/2012); (iii) Pesticides (Regulation (EC) No 1107/2009); and (iv) Veterinary medicines (Regulation (EU) 2019/6)). As a part of the Green Deal, the Commission has proposed a 'one-substance one-assessment' (OS-OA) approach for chemicals[19], in order to increase the efficiency of the registration system, reduce costs and unnecessary animal testing.

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

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13 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).

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

15 Directive 2006/118/EC of the European Parliament and of the Council of 12 December 2006 on the protection of groundwater against pollution and deterioration (OJ L 372, 27.12.2006, p. 19).

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

17 Directive (EU) 2020/2184 of the European Parliament and of the Council of 16 December 2020 on the quality of water intended for human consumption (recast) (OJ L 435, 23.12.2020, p. 1).

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

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

cover the risk of AMR selection during the entire life cycle of antimicrobials, including manufacturing.

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

(74) For medicinal products authorised prior to October 2005, without any ERA, specific provisions should be introduced to set up a risk based prioritisation programme for the ERA submission or update by the market authorisation holders.

(75) Cyprus, Ireland, Malta and Northern Ireland have historically relied on the supply of medicinal products from or through parts of the United Kingdom other than Northern Ireland. Following the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community, to prevent shortages of medicinal products and ultimately to ensure a high level of public health protection, specific derogations to this Directive need to be included for medicinal products supplied to Cyprus, Ireland, Malta and Northern Ireland from or through parts of the United Kingdom other than Northern Ireland. In order to ensure uniform application of Union law in the Member States, the derogations applicable in Cyprus, Ireland and Malta should be of a temporary nature only.

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

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

(78) To avoid unnecessary administrative and financial burdens both for the marketing authorisation holders and the competent authorities, certain streamlining measures should be introduced, in line with the digital by default principle. Electronic application for marketing authorisation and for variations to the terms of the marketing authorisation should be introduced.

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

(80) In the event of a risk to public health, the marketing authorisation holder or the competent authorities should be able to make urgent safety or efficacy restrictions on their own

initiative. In such case, when the referral procedure is launched, any duplication of assessment should be avoided.

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

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

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

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

(85) The Directive also clarifies that a medical device that is part of an integral combination has to comply with the general safety and performance requirements set out in Annex I of Regulation (EU) 2017/745 of the European Parliament and of the Council[20]. A medical device in exclusive use with a medical device needs to meet all of the requirements of Regulation (EU) 2017/745. A medicinal product in exclusive use with a medical device that is not ancillary to that of the medical device shall comply with the requirements of this Directive and of the [revised Regulation (EC) No 726/2004] taking into account its use with the medical device, without prejudice to the specific requirements of the Regulation (EU) 2017/745.

[20] 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).

(86) For all these products (integral combinations of a medicinal product and a medical device, medicinal products in exclusive use with medical devices and combinations of a medicinal product with a product other than a medical device) the competent authority should also be able to request the marketing authorisation applicant to transmit any additional information needed and the marketing authorisation applicant should be bound to submit any such information requested. For medicinal product in exclusive use with a medical device that is not ancillary to that of the medical device, the marketing authorisation applicant shall also, upon request from the competent authority, submit any additional information related to the medical device taking into account its use with the medicinal product and that is relevant for the post-authorisation monitoring of the medicinal product, without prejudice to the specific requirements of the [revised Regulation (EC) No 726/2004].

(87) For integral combination of a medicinal product with a medical device and for combinations of a medicinal product with a product other than a medical device, the marketing authorisation holder should also bear the overall responsibility for the whole product in terms of compliance of the medicinal product with the requirements of this Directive and the [revised Regulation(EC) No 726/2004] and should ensure coordination of the information flow between the sectors throughout the assessment procedure and the lifecycle of the medicinal product.

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

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

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

(91) The adaptations may entail adapted, enhanced, waived or deferred requirements compared to standard medicinal products. They could in particular include changes to the dossier requirements for such medicinal products, the way their quality, safety and efficacy is demonstrated by applicants or tailored manufacturing controls and good manufacturing practices requirements, as well as additional control methods prior and during their administration and use. The adaptions should however not go beyond what is necessary for the attainment of the objective of adaptation to the specific characteristics.

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

(93) To optimise the use of resources for both applicants for marketing authorisation and competent authorities and avoid duplication of assessment of chemical active substances of medicinal products, marketing authorisation applicants should be able to rely on an active substance master file certificate or a monograph of the European Pharmacopeia, instead of submitting the relevant data as required in accordance with Annex II. An active substance master file certificate may be granted by the Agency when the relevant data on the active substance concerned is not already covered by a monograph of the European Pharmacopeia or by another active substance master file certificate. The Commission should be empowered to establish the procedure for the single assessment of an active substance master file. To further optimise the use of resources, the Commission should be empowered to allow use a certification scheme also for additional quality master files i.e. for active substances other than chemical active substances, or for other substances present or used in the manufacture of a medicinal product, required in accordance with Annex II, e.g. in case of novel excipients, adjuvants, radiopharmaceutical precursors and active substance intermediates, when the intermediate is a chemical active substance by itself or used in conjugation with a biological substance.

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

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

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

(97) 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 further enable data-driven benefit-risk assessments at all stages of the lifecycle of a medicinal product. This Directive therefore empowers competent authorities of Member States to request such data as part of the assessment of initial and post-marketing authorisation applications.

Due to the sensitive nature of health data, the competent authorities should safeguard its processing operations and ensure that they respect the data protection principles of lawfulness, fairness and transparency, purpose limitation, data minimisation, accuracy, storage limitation, integrity and confidentiality. Where the processing of personal data is necessary for the purposes of this Directive, such processing should be done in accordance with Union law on the protection of personal data. Any processing of personal data under this Directive should take place in accordance with Regulation (EU) 2016/679[21] and Regulation (EU) 2018/1725[22] of the European Parliament and of the Council.

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

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

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

(101) The increasing use of electronic networks for communication of information on adverse reactions to medicinal products marketed in the Union is intended to allow competent authorities to share the information at the same time.

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

(103) Marketing authorisation holders should be proactively responsible for on-going pharmacovigilance of the medicinal products they place on the market.

(104) The use of colours in human and veterinary medicinal products is currently regulated by Directive 2009/35/EC of the European Parliament and of the Council[23], and restricted to those authorised in accordance with Regulation (EC) No 1333/2008 of the European Parliament and of the Council on food additives[24], for which specifications are laid down in Commission Regulation (EU) No 231/2012[25]. Uses of excipients other than colours in

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21 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).

22 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).

23 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).

24 Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives (OJ L 354, 31.12.2008, p. 16).

25 Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council (OJ L 83, 22.3.2012, p. 1).

medicinal products are subject to the Union rules on medicinal products and are evaluated as part of the overall benefit risk profile of a medicinal product.

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

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

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

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

(109) There may be cases where manufacturing or testing steps of medicinal products need to take place in sites close to patients, for example advanced therapy medicinal products with short shelf-life. In such cases, these manufacturing or testing steps may need to be decentralised to multiple sites to reach patients across the Union. When the manufacturing or testing steps are decentralised, they should be carried out under the responsibility of the qualified person of an authorised central site. The decentralised sites should not require a separate manufacturing authorisation from the one granted to the relevant central site but should be registered by the competent authority of the Member State in which the decentralised site is established. In the case of medicinal products containing, consisting or derived from autologous SoHO, the decentralised sites have to be registered as a SoHO entity as defined in and pursuant to [SoHO Regulation] for the activities of donor review and eligibility assessment, donor testing and collection, or just for collection in the case of products manufactured for autologous use.

(110) The quality of medicinal products manufactured or available in the Union should be guaranteed by requiring that the active substances used in their composition comply with the principles of good manufacturing practice in relation to those medicinal products. It has proved necessary to reinforce the Union provisions on inspections and to compile a Union database of the results of those inspections.

(111) Verification of compliance with the legal requirements of manufacturing, distribution and use of medicinal products by relevant entities through a system of supervision, is of fundamental importance to ensure that the objectives of this Directive are effectively achieved. Therefore, the competent authorities of the Member States should have the power to perform on site or remote inspections, as part of the system of supervision at all stages of manufacturing, distribution and use of medicinal products or active substances and rely on the outcome of inspections conducted by trusted third countries competent authorities. To

preserve the effectiveness of the inspections, the competent authorities should have the possibility to perform joint inspections and also, where necessary, unannounced inspections.

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

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

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

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

(116) In this connection persons moving around within the Union have the right to carry a reasonable quantity of medicinal products lawfully obtained for their personal use. It should also be possible for a person established in one Member State to receive from another Member State a reasonable quantity of medicinal products intended for their personal use.

(117) By virtue of [revised Regulation (EC) No 726/2004], certain medicinal products are the subject of a Union marketing authorisation. In this context, the prescription status of medicinal products covered by a Union marketing authorisation needs to be established. It is therefore important to set the criteria on the basis of which Union decisions will be taken.

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

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

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

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

(122) Marketing authorisation is to be subject to certain essential conditions and it is the responsibility of the Member State concerned to ensure that such conditions are met; whereas each Member State is to recognize authorisations granted by other Member States.

(123) Certain Member States impose on wholesalers who supply medicinal products to pharmacists and on persons authorised to supply medicinal products to the public certain public service obligations. Those Member States should be able to continue to impose those obligations on wholesalers established within their territory. They should also be able to impose them on wholesalers in other Member States on condition that they do not impose any obligation more stringent than those that they impose on their own wholesalers and provided that such obligations may be regarded as warranted on grounds of public health protection and are proportionate in relation to the objective of such protection.

(124) Rules should be laid down as to how the labelling and package leaflets are to be presented.

(125) The provisions governing the information supplied to users should provide a high degree of consumer protection, in order that medicinal products may be used correctly on the basis of full and comprehensible information.

(126) The marketing of medicinal products whose labelling and package leaflets comply with this Directive should not be prohibited or impeded on grounds connected with the labelling or package leaflet.

(127) The use of electronic and technological possibilities other than paper package leaflets can facilitate access to medicinal products, medicinal products distribution and should always guarantee equal or better quality of information to all patients compared to the paper form of product information.

(128) Member States have varying levels of digital literacy and internet access. In addition, patient and healthcare professional needs may differ. It is therefore necessary that Member States have a discretion on the adoption of measures enabling the electronic provision of product information while ensuring that no patient is left behind, taking into account the needs of different age categories and the different levels of digital literacy in the population, and making sure that product information is easily accessible to all patients. Member States should progressively allow the possibility for electronic product information, while ensuring full compliance with the rules on protection of personal data, and adhere to harmonised standards developed at EU level.

(129) Where Member States decide that the package leaflet should be made available in principle only electronically, they should also ensure that a paper version of the package leaflet is to be made available on demand and without additonal cost to patients. They should also

ensure that the information in digital format is easily accessible to all patients, for instance by including in the outer packaging of the product a digitally readable barcode, which would direct the patient to the electronic version of the package leaflet.

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

(131) To ensure a high level of transparency of public support to the research and development of medicinal products, the reporting of public contribution for the development of a particular medicinal product should be a requirement for all medicines. Given however the practical difficulty to identify how indirect public funding instruments, such as tax advantages, have supported a particular product, the reporting obligation should only concern the direct public financial support, such as direct grants or contracts. Therefore, the provisions of this Directive ensure, without prejudice to the rules on the protection of confidential and personal data, transparency regarding any direct financial support received from any public authority or public body to carry out any activities for the research and development of medicinal products.

(132) To ensure the accuracy of the information made publicly available by the marketing authorisation holder, the declared information has to be subject to audit by an independent auditor.

(133) In order to ensure a harmonised and consistent reporting of public contribution for the development of a particular medicinal products, the Commission should be able to adopt implementing acts to clarify the principles and format that the marketing authorisation holder should adhere to when reporting this information.

(134) This Directive is without prejudice to the application of measures adopted pursuant to Directive 2006/114/EC of the European Parliament and of the Council[26] or pursuant to Directive 2005/29/EC of the European Parliament and of the Council[27]. Therefore the provisions regarding the advertising of medicinal products of this Directive should therefore be considered, where relevant, as a *lex specialis* with respect to Directive 2005/29/EC.

(135) Advertising, even of medicinal products not subject to a prescription, could affect public health and distort competition. Therefore, advertising of medicinal products should meet certain criteria. Persons qualified to prescribe, administer or supply medicinal products can properly evaluate the information available in advertising because of their knowledge, training and experience. The advertising of medicinal products to persons who cannot properly assess the risk associated with their use may lead to medicinal product misuse or overconsumption which is liable to harm public health.

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[26] Directive 2006/114/EC of the European Parliament and of the Council of 12 December 2006 concerning misleading and comparative advertising (OJ L 376, 27.12.2006, p. 21).

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

Therefore advertisement to the general public of medicinal products that are available only on medical prescription should be prohibited. Furthermore, distribution of samples free of charge to the general public for promotional ends is to be prohibited, also teleshopping for medicinal products shall be prohibited pursuant to Directive 2010/13/EU of the European Parliament and of the Council[28]. It should be possible within certain restrictive conditions to provide samples of medicinal products free of charge to persons qualified to prescribe or supply them so that they can familiarise themselves with new products and acquire experience in dealing with them.

(136) Advertising of medicinal products should aim at disseminating objective and unbiased information about the medicinal product. For that purpose, it is expressly forbidden highlight negatively another medicinal product or to suggest that advertised medicinal product might be safer or more effective than another medicinal product. Comparison of medicinal products should only be allowed if such information is listed in the summary of product characteristics of the medicinal product being advertised. This prohibition covers any medicinal product, also biosimilars, and therefore it would be misleading to refer in the advertising, that a biosimilar medicinal product would not be interchangeable with the original biological medicinal product or another biosimilar from the same original biological medicinal product. Additional strict rules about negative and comparative advertising of competitor medicinal products will prohibit claims that can mislead persons qualified to prescribe, administer or supply them.

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

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

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

(140) Innovative, ‘combination medicinal products’ and other developed medicinal products are complex in regards to their composition and administration. Therefore, in addition to persons qualified to prescribe medicinal products, also persons qualified to administer medicinal products need to be familiar with all characteristics of those medicinal products, especially with safe administration and use, including the comprehensive instructions to the patients. For that purpose information about medicinal products subject to medical prescription is also clearly allowed to persons qualified to administer them.

(141) Persons qualified to prescribe, administer or supply medicinal products should have access to a neutral, objective source of information about products available on the market.

[28] Directive 2010/13/EU of the European Parliament and of the Council of 10 March 2010 on the coordination of certain provisions laid down by law, regulation or administrative action in Member States concerning the provision of audiovisual media services (Audiovisual Media Services Directive) (OJ L 095 15.4.2010, p. 1).

Whereas it is nevertheless for the Member States to take all measures necessary to this end, in the light of their own particular situation.

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

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

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

(145) In order to ensure uniform conditions for the implementation of this Regulation, implementing powers should be conferred on the Commission. Those powers should be exercised in accordance with Regulation (EU) No 182/2011 of the European Parliament and of the Council[29].

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

(147) On the basis of the opinion of the Agency, the Commission should adopt a decision on the referral by means of implementing acts. In justified cases, the Commission may return the opinion for further examination or deviate in its decision from the opinion of the Agency.

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[29] 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).

Taking into account the need to make medicinal products swiftly available to patients, it should be acknowledged that the chairperson of the Standing Committee for Medicines for Human Use will use the available mechanisms under Regulation 182/2011 and notably the possibility to obtain the committees opinion in written procedure and within expeditious deadlines which, in principle, will not exceed 10 calendar days.

(148) The Commission should be empowered to adopt any necessary changes to Annex II in order to take into account scientific and technical progress.

(149) In order to supplement or amend certain non-essential elements of this Directive, the power to adopt acts in accordance with Article 290 TFEU should be delegated to the Commission in respect of specifying the procedure for examination of application of active substance master file certificate, the publication of such certificates, the procedure for changes to the active substance master file and its certificate, access to the active substance master file and its assessment report; specifying additional quality master files to provide information on a constituent of a medicinal product, the procedure for examination of application of a quality master file certificate, the publication of such certificates, the procedure for changes to the quality master file and its certificate, and access to the quality master file and its assessment report; determining the situations in which post-authorisation efficacy studies may be required; specifying the 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. It is of particular importance that the Commission carry out appropriate consultations during its preparatory work, including at expert level, and that those consultations be conducted in accordance with the principles laid down in the Interinstitutional Agreement of 13 April 2016 on Better Law-Making[30]. 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.

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

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

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

(152) In accordance with the Joint Political Declaration of 28 September 2011 of Member States and the Commission on explanatory documents[31], Member States have undertaken to accompany, in justified cases, the notification of their transposition measures with one or more documents explaining the relationship between the components of a directive and the corresponding parts of national transposition instruments. With regard to this Directive, the legislator considers the transmission of such documents to be justified.

HAVE ADOPTED THIS DIRECTIVE:

Chapter I:
Subject matter, scope and definitions

Article 1

Subject matter and scope

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

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

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

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

5. The Directive shall not apply to:

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

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

(b) medicinal product prepared in a pharmacy in accordance with a pharmacopoeia and intended to be supplied directly to the patients served by the pharmacy in question (‘officinal formula’);

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

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

7. Member States shall take the necessary measures to develop the production and use of medicinal products derived from substances of human origin coming from voluntary unpaid donations.

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

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

10. This Directive shall not affect the application of national legislation prohibiting or restricting the following:

(a) the sale, supply or use of medicinal products as contraceptives or abortifacients;

(b) the use of any specific type of substance of human origin or animal cells, on grounds not dealt with in the aforementioned Union law;

(c) the sale, supply or use of medicinal products containing, consisting of or derived from these animal cells or substances of human origin, on grounds not dealt with in Union law.

Article 2

Advanced therapy medicinal products prepared under hospital exemption

1. By way of derogation from Article 1(1), only this Article shall apply to advanced therapy medicinal products prepared on a non-routine basis in accordance with the requirements set in paragraph 3 and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient (‘advanced therapy medicinal products prepared under hospital exemption’).

2. The manufacturing of an advanced therapy medicinal product prepared under hospital exemption shall require an approval by the competent authority of the Member State

(‘hospital exemption approval’). Member States shall notify any such approval, as well as subsequent changes, to the Agency.

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

3. Member States shall ensure that advanced therapy medicinal products prepared under hospital exemption comply with the requirements equivalent to the good manufacturing practices and traceability for advanced therapy medicinal products referred to in Articles 5 and 15 of Regulation (EC) No 1394/2007 [32] respectively, and with pharmacovigilance requirements equivalent to those provided for at Union level pursuant to [revised Regulation (EC) No 726/2004].

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

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

6. The competent authority of the Member State shall transmit the data related to the use, safety and efficacy of an advanced therapy medicinal product prepared under the hospital exemption approval to the Agency annually. The Agency shall, in collaboration with the competent authorities of Member States and the Commission, set up and maintain a repository of that data.

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

   (a) details of the application for the approval of hospital exemption referred to in paragraph 1, second subparagraph, including the evidence on quality, safety and efficacy of the advance therapy medicinal products prepared under hospital exemption for the approval and the subsequent changes;

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

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

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

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

8. The Agency shall provide to the Commission a report on the experience acquired with the hospital exemption approvals on the basis of contributions from Member States and the data referred to in paragraph 4. The first report shall be provided three years after [OP

[32] Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 1).

please insert the date =18 months after the date of entering into force of this Directive] and then every five years thereafter.

Article 3

Exceptions under certain circumstances

1. A Member State may, in order to fulfil special needs, exclude from the scope of this Directive medicinal products supplied in response to a bona fide unsolicited order, prepared in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under their direct personal responsibility. However, in such case Member States shall encourage healthcare professionals and patients to report data on the safety of the use of such products to the competent authority of the Member State in accordance with Article 97.

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

2. Without prejudice to Article 30 of [revised Regulation (EC) No 726/2004], Member States may temporarily authorise the use and distribution of an unauthorised medicinal product in response to a suspected or confirmed spread of pathogenic agents, toxins, chemical agents or nuclear radiation any of which could cause harm.

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

4. Liability for defective products, as provided for by [Council Directive 85/374/EEC[33] – OP please replace reference by new instrument COM(2022) 495 when adopted], shall not be affected by paragraph 3.

Article 4

Definitions

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

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

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

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

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

(2) ‘substance’ means any matter irrespective of origin, which may be:

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

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

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

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

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

(f) fungi, including micro-fungi (yeast);

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

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

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

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

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

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

(9) ‘competent authorities’ means the Agency and the competent authorities of the Members States;

(10) ‘Agency’ means the European Medicines Agency;

(11) ‘non-clinical’ means a study or a test conducted in vitro, in silico, or in chemico, or a non-human in vivo test related to the investigation of the safety and efficacy of a medicinal product. Such test may include simple and complex human cell-based

assays, microphysiological systems including organ-on-chip, computer modelling, other non-human or human biology-based test methods, and animal-based tests;

(12) ‘reference medicinal product’ means a medicinal product that is or has been authorised in the Union under Article 5, in accordance with Article 6;

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

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

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

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

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

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

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

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

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

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

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

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

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

(24) ‘combined advanced therapy medicinal products’ means a product as defined in Article 2 of Regulation (EC) No 1394/2007, including when a gene therapy medicinal product is part of the combined advanced therapy medicinal product;

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

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

(27) ‘immunological medicinal product’ means:

(a) any vaccine or allergen product, or

(b) any medicinal product consisting of toxins or serums used to produce passive immunity or to diagnose the state of immunity;

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

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

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

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

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

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

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

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

(31) ‘SoHO-derived medicinal product other than ATMPs’ means any medicinal product containing, consisting of or deriving from a substance of human origin (SoHO), as defined in Regulation [SoHO Regulation], other than tissues and cells, that is of standardised consistency and is prepared by:

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

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

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

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

(34) 'antimicrobial resistance' means the ability of a micro-organism to survive or to grow in the presence of a concentration of an antimicrobial agent that is usually sufficient to inhibit or kill that micro-organism;

(35) 'risks related to use of the medicinal product' means any risk:

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

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

(c) of undesirable effects on public health due to the release of the medicinal product in the environment including anti-microbial resistance;

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

(37) 'paediatric investigation plan' means a research and development programme aimed at ensuring that the necessary data are generated determining the conditions in which a medicinal product may be authorised to treat the paediatric population;

(38) 'paediatric population' means that part of the population aged between birth and 18 years;

(39) 'medicinal prescription' means any medicinal prescription issued by a professional person qualified to do so;

(40) 'abuse of medicinal products' means persistent or sporadic, intentional excessive use of medicinal products that is accompanied by harmful physical or psychological effects;

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

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

(43) ‘package leaflet’ means information for the user that accompanies the medicinal product;

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

(45) ‘immediate packaging’ means the container or other form of packaging immediately in contact with the medicinal product;

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

(47) ‘name of the medicinal product’ means the name, which may be either an invented name not liable to confusion with the common name, or a common or scientific name accompanied by a trademark or by the name of the marketing authorisation holder;

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

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

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

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

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

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

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

(51) ‘public health emergency’ means a public health emergency recognised at Union level by the Commission under Article 23(1) of Regulation (EU) 2022/2371 of the European Parliament and of the Council[34];

(52) ‘entity not engaged in an economic activity’ means any legal or natural person that is not engaged in an economic activity and that:

(a) is not an undertaking or controlled by an undertaking; and,

[34] 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).

(b) has not concluded any agreements with any undertaking concerning sponsorship or participation to the medicinal product development;

(53) 'micro, small and medium-sized enterprises' means micro, small and medium-sized enterprises as defined in Article 2 of Commission Recommendation 2003/361/EC[35];

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

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

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

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

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

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

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

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

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

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

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

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

(63) ‘traditional herbal medicinal product’ means a herbal medicinal product that fulfils the conditions laid down in Article 134(1);

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

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

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

(67) ‘corresponding traditional herbal medicinal product’ means a traditonal herbal medicinal product with the same active substances, irrespective of the excipients used, the same or similar intended purpose, equivalent strength and posology and the same or similar route of administration as the traditional herbal medicinal product applied for;

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

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

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

2. The Commission is empowered to adopt delegated acts in accordance with Article 215 to amend the definitions in paragraph 1, points (2) to (6), (8), (14), (16) to (31), in the light of technical and scientific progress and taking into account definitions agreed at Union and international level without extending the scope of the definitions.

Chapter II
Application requirements for national and centralised marketing authorisations

SECTION 1

GENERAL PROVISIONS

Article 5

Marketing authorisations

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

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

Article 6

General requirements for marketing authorisation applications

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

2. The marketing authorisation application shall include the particulars and documentation listed in Annex I, submitted in accordance with Annex II.

3. The documents and information concerning the results of the pharmaceutical and non-clinical tests and the clinical studies referred to in Annex I shall be accompanied by detailed summaries in accordance with Article 7 and supportive raw data.

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

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

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

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

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

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

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

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

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

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

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

Article 7

Expert verification

1. The marketing authorisation applicant shall ensure that the detailed summaries referred to in Article 6(3) have been drawn up and signed by experts with the necessary technical or professional qualifications before they are submitted to the competent authorities. The technical or professional qualifications of the experts shall be set out in a brief curriculum vitae.

2. The experts referred to in paragraph 1 shall justify any use made of scientific literature under Article 13 in accordance with the requirements set out in Annex II.

Article 8

Medicinal products manufactured outside the Union

Member States shall take all appropriate measures to ensure that:

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

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

SECTION 2

SPECIFIC REQUIREMENTS FOR ABRIDGED APPLICATIONS FOR MARKETING AUTHORISATION

Article 9

Applications concerning generic medicinal products

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

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

3. Paragraph 1 shall also apply if the reference medicinal product has not been authorised in the Member State in which the application for the generic medicinal product is submitted. In this case, the applicant shall indicate in the application the name of the Member State in which the reference medicinal product is or has been authorised. At the request of the competent authority of the Member State in which the application is submitted, the competent authority of the other Member State shall transmit within a period of one month

a confirmation that the reference medicinal product is or has been authorised together with the full composition of the reference medicinal product and if necessary, any other relevant documentation.

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

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

5. Where there is a significant difference in properties as referred to in paragraph 4, the applicant shall submit additional information in order to prove the safety or efficacy of the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the authorised active substance of the reference medicinal product in an application under Article 10.

Article 10

Applications concerning hybrid medicinal products

In cases where the medicinal product does not fall within the definition of a generic medicinal product or has changes in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference medicinal product, the results of the appropriate non-clinical tests or clinical studies shall be provided to the competent authorities to the extent necessary to establish a scientific bridge to the data relied upon in the marketing authorisation for the reference medicinal product, and to demonstrate the safety and efficacy profile of the hybrid medicinal product.

Article 11

Applications concerning biosimilar medicinal products

For a biological medicinal product that is similar to a reference biological medicinal product (‘biosimilar medicinal product’), the results of appropriate comparability tests and studies shall be provided to the competent authorities. The type and quantity of supplementary data to be provided must comply with the relevant criteria stated in Annex II and the related detailed guidelines. The results of other tests and studies from the reference medicinal product's dossier shall not be provided.

Article 12

Applications concerning bio-hybrid medicinal products

In cases where a biosimilar medicinal product has changes in strength, pharmaceutical form, route of administration or therapeutic indications, compared to the reference biological medicinal product (‘bio-hybrid’), the results of the appropriate non-clinical tests or clinical studies shall be provided to the competent authorities to the extent necessary to establish a scientific bridge to the data relied upon in the marketing authorisation for the reference biological medicinal product, and to demonstrate the safety or efficacy profile of the biosimilar medicinal product.

Article 13

Applications based on bibliographic data

In cases where no reference medicinal product is or has been authorised for the active substance of the medicinal product concerned, the applicant shall, by way of derogation from Article 6(2), not be required to provide the results of non-clinical tests or clinical studies if the applicant can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Union for the same therapeutic use and route of administration and for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex II. In that event, the test and trial results shall be replaced by appropriate bibliographic data in the form of scientific literature.

Article 14

Applications based on consent

Following the granting of a marketing authorisation, the marketing authorisation holder may, by letter of access, allow use to be made of all documentation referred to in Article 6(2) with a view to examining subsequent applications relating to other medicinal products possessing the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form.

SECTION 3

SPECIFIC REQUIREMENTS FOR APPLICATIONS FOR CERTAIN CATEGORIES OF MEDICINAL PRODUCTS

Article 15

Fixed dose combination medicinal product, platform technologies and multi-medicinal product packages

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

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

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

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

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

Article 16

Radiopharmaceuticals

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

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

Article 17

Antimicrobials

1. Where the application for a marketing authorisation concerns an antimicrobial, the application shall, in addition to the information referred to in Article 6, contain the following:

   (a) an antimicrobial stewardship plan as referred to in Annex I;

   (b) a description of the special information requirements outlined in Article 69 and listed in Annex I.

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

3. The marketing authorisation holder shall ensure that the pack size of the antimicrobial corresponds to the usual posology and duration of treatment.

Article 18

Integral combinations of medicinal products and medical devices

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

As part of the assessment, in accordance with Article 29, of the integral combination of a medicinal product and a medical device the competent authorities shall assess the benefit-risk balance of the integral combination of a medicinal product and a medical device, taking into account the suitability of the use of the medicinal product together with the medical device.

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

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

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

5. The marketing authorisation applicant shall, upon request from the competent authority, submit any additional information related to the medical device and that is relevant for the benefit-risk balance assessment of the integral combination of a medicinal product with a medical device referred to in paragraph 1.

Article 19

Medicinal products in exclusive use with medical devices

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

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

2. For medicinal products in exclusive use with a medical device the medical device shall meet the requirements set out in Regulation (EU) 2017/745.

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

4. In its evaluation of the medicinal product referred to in paragraph 1 the competent authority shall recognise the results of the assessment of compliance of the medical device concerned with the general safety and performance requirements in accordance with Annex I of Regulation (EU) 2017/745 including, where relevant, the results of the assessment by a notified body.

5. The marketing authorisation applicant shall, upon request from the competent authority, submit any additional information related to the medical device and that is relevant for the benefit-risk balance assessment of the medicinal product referred to in paragraph 1, taking into account the use of the medicinal product with the medical device.

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

In this case, the marketing authorisation applicant shall, upon request from the competent authorities, submit any additional information related to the medical device, taking into account its use with the medicinal product and that is relevant for the post-authorisation monitoring of the medicinal product, without prejudice to the specific requirements of the [revised Regulation (EC) No 726/2004].

Article 20

Combinations of medicinal products with products other than medical devices

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

As part of the assessment, in accordance with Article 29, of the combination of a medicinal product with a product other than a medical device the competent authority shall assess the benefit-risk balance of the combination of a medicinal product and a product other than a medical device, taking into account the use of the medicinal product together with the other product.

2. The marketing authorisation applicant shall, upon request from the competent authority submit any additional information related to the product other than medical devices and that is relevant for the benefit-risk balance assessment of the combination of medicinal products with the product other than medical devices, taking into account the suitability of the use of the medicinal product with the product referred to in paragraph 1.

SECTION 4

SPECIFIC DOSSIER REQUIREMENTS

Article 21

Risk management plan

The applicant of a marketing authorisation for a medicinal product referred to in Articles 9 and 11 shall not be required to submit a risk management plan and a summary thereof, provided that no additional risk minimisation measures exist for the reference medicinal product and provided that the marketing authorisation for the reference medicinal product has not been withdrawn prior to the submission of the application.

Article 22

Environmental risk assessment and other environmental information

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

2. The ERA shall indicate whether the medicinal product or any of its ingredients or other constituents is one of the following substances according to the criteria of Annex I to the Regulation (EC) No 1272/2008:

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

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

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

   or are endocrine active agents.

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

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

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

6. The marketing authorisation holder shall update the ERA with new information without undue delay to the relevant competent authorities, in accordance with Article 90(2), if new information pertaining to the assessment criteria referred to in Article 29 becomes available and could lead to a change of the conclusions of the ERA. The update shall include any relevant information from environmental monitoring, including monitoring under Directive 2000/60/EC, from eco-toxicity studies, from new or updated risk

assessments under other Union legislation, as referred to in paragraph 1, and environmental exposure data.

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

7. For medicinal products referred to in Articles 9 to 12, the applicant may refer to ERA studies conducted for the reference medicinal product when preparing the ERA.

Article 23

ERA of medicinal products authorised before 30 October 2005

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

   This programme shall be made publicly available by the Agency.

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

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

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

Article 24

System of ERA monographs of the ERA data of active substances

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

physiochemical data, fate data and effect data based on an assessment of a competent authority.

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

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

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

5. The Commission is empowered to adopt delegated acts in accordance with Article 215 and based on the results of a proof-of-concept pilot referred to in paragraph 4, to supplement this Directive by specifying the following:

   (a) the content and format of ERA monographs;

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

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

   (d) the risk-based prioritisation criteria for the selection and prioritisation referred to in paragraph 2;

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

Article 25

Active substance master file certificate

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

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

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

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

The Agency shall establish a repository of active substance master files, their assessments reports and their certificates and ensure that personal data is protected. The Agency shall ensure that the competent authorities of the Member State have access to this repository.

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

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

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

6. If requested by the Agency, the manufacturer of the substance for which an application for an active substance master file certificate has been submitted or the active substance master file certificate holder shall undergo an inspection to verify the information contained in the application or the active substance master file or their compliance with good manufacturing practices for active substances referred to in Article 160.

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

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

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

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

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

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

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

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

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

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

Article 26

Additional quality master files

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

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

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

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

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

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

   (c) the rules for the examination of applications for making publicly available of additional quality master file certificates;

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

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

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

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

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

Article 27

Excipients

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

   Excipients shall be examined by the competent authorities as part of the medicinal product.

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

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

   (b) the list established by the Commission pursuant to paragraph 3.

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

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

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

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

   The list of colours permitted for use in medicinal products shall be established by way of implementing acts. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 214(2).

4. If a colour used in medicinal product is removed from the Union list of authorised food additives, on the basis of the scientific opinion of the European Food Safety Authority ('EFSA'), the Agency shall, on the request of the Commission or on its own initiative, without undue delay issue a scientific opinion as regards the use of the colour concerned in medicinal product, taking into account the opinion of the EFSA if relevant. The opinion of the Agency shall be adopted by the Committee for Medicinal Products for Human Use.

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

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

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

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

7. Paragraphs 2 to 6 shall also apply to colours used in veterinary medicinal products as defined in Article 4(1) of Regulation (EU) 2019/6 of the European Parliament and of the Council [36].

SECTION 5

ADAPTED DOSSIER REQUIREMENTS

Article 28

Adapted frameworks due to the characteristics or methods inherent to the medicinal product

1. Medicinal products listed in Annex VII shall be subject to specific scientific or regulatory requirements due to the characteristics or methods inherent to the medicinal product, when:

   (a) it is not possible to adequately assess the medicinal product or category of medicinal products applying the applicable requirements due to scientific or regulatory challenges arising from characteristics or methods inherent to the medicinal product; and

   (b) the characteristics or methods positively impact the quality, safety and efficacy of the medicinal product or category of medicinal product or provide a major contribution to patient access or patient care.

2. The Commission is empowered to adopt delegated acts in accordance with Article 215 to amend Annex VII in order to take account of scientific and technical progress.

3. The Commission is empowered to adopt delegated acts in accordance with Article 215 to supplement this Directive by laying down:

   (a) detailed rules for the marketing authorisation and supervision of the medicinal products referred to in paragraph 1;

   (b) the technical documentation to be submitted by applicants for marketing authorisations for medicinal products referred to in paragraph 1.

[36] 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.

4. The detailed rules referred to in paragraph 3, point (a), shall be proportionate to the risk and impact involved. These may entail adapted, enhanced, waived or deferred requirements. Any waiver or deferral shall be limited to the extent strictly necessary, proportionate and duly justified by the characteristics or methods inherent to the medicinal product, and shall be regularly reviewed and evaluated. Apart from the detailed rules referred to in paragraph 3, point (a), all other rules laid out in this Directive shall apply.

5. Until the adoption of detailed rules for specific medicinal products listed in Annex VII pursuant to paragraph 3, an application for a marketing authorisation for that medicinal product may be submitted in accordance with Article 6(2).

6. When adopting delegated acts referred to in this Article, the Commission shall take into account any available information resulting from a regulatory sandbox established in accordance with Article 115 of the [revised Regulation (EC) No 726/2004].

Chapter III
Procedures for national marketing authorisations

SECTION 1

GENERAL PROVISIONS

Article 29

Examination of marketing authorisation application

1. In order to examine an application submitted in accordance with Articles 6 and 9 to 14, the competent authority of the Member State:

   (a) shall verify whether the particulars and documentations submitted in support of the application comply with Articles 6 and 9 to 14 ('validation'), and examine whether the conditions for issuing a marketing authorisation set out in Articles 43 to 45 are complied with;

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

   (c) may, where appropriate, require the applicant to supplement the particulars accompanying the application in respect of the items listed in the Articles 6 and 9 to 14;

   (d) may consider and decide upon additional evidence available, independently from the data submitted by the marketing authorisation applicant.

2. Where the competent authority of the Member State avails itself of the option referred to in the first subparagraph, point (c), the time limits laid down in Article 30 shall be suspended until such time as the supplementary information required has been provided or for the time allowed to the applicant for giving oral or written explanations.

3. Where the competent authority of the Member State considers that the marketing authorisation application is incomplete, or contains critical deficiencies that may prevent the evaluation of the medicinal product it shall inform the applicant accordingly and shall set a time limit for submitting the missing information and documentation. If the applicant fails to provide the missing information and documentation within the time limit set, the application shall be considered to have been withdrawn.

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

The competent authority of the Member State shall summarise the deficiencies in writing. On this basis, the competent authority of the Member State shall inform the applicant accordingly and set a time limit to address the deficiencies. The application shall be suspended until the applicant addresses the deficiencies. If the applicant fails to address those deficiencies within the time limit set by the competent authority of the Member State, the application shall be considered as withdrawn.

Article 30

Duration of examination of marketing authorisation application

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

Article 31

Types of national marketing authorisation procedures

National marketing authorisations may be granted in accordance with the procedures laid down in Article 32 (‘purely national marketing authorisation procedure’), Articles 33 and 34 (‘decentralised procedure for national marketing authorisation’) or Articles 35 and 36 (‘mutual recognition procedure for national marketing authorisation’).

SECTION 2

MARKETING AUTHORISATIONS VALID IN A SINGLE MEMBER STATE

Article 32

Purely national marketing authorisation procedure

1. An application for marketing authorisation according to Article 6(2) under the purely national marketing authorisation procedure shall be submitted to the competent authority in that Member State in which the marketing authorisation is applied.

2. The competent authority in the Member State concerned shall examine the application in accordance with Articles 29 and 30 and grant a marketing authorisation in accordance with Articles 43 to 45 and applicable national provisions.

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

SECTION 3

MARKETING AUTHORISATIONS VALID IN SEVERAL MEMBER STATES

Article 33

Scope of decentralised procedure for national marketing authorisations

1. An application for marketing authorisation under the decentralised procedure for national marketing authorisation in several Member States in respect of the same medicinal product shall be submitted to the competent authorities in those Member States in which the marketing authorisation is applied.

2. The competent authorities in the Member State concerned shall examine the applications in accordance with Articles 29, 30 and 34 and grant a marketing authorisation in accordance with Articles 43 to 45.

3. Where a competent authority of the Member State notes that another marketing authorisation application for the same medicinal product is being examined by the competent authority in another Member State, the competent authorities of the Member States concerned shall decline to examine the application and shall advise the applicant that the provisions referred to in Articles 35 and 36 apply.

4. Where the competent authorities of the Member States are informed that another Member State has authorised a medicinal product that is the subject of a marketing authorisation application in the Member State concerned, they shall reject the application unless it was submitted in compliance with the provisions referred to in Articles 35 and 36.

5. Marketing authorisations granted under decentralised procedure for national marketing authorisation shall be valid only in those Member States of the competent authority that granted it.

Article 34

Decentralised procedure for national marketing authorisations

1. With a view to obtain a national marketing authorisation for a medicinal product in several Member States in respect of the same medicinal product under the decentralised procedure for national marketing authorisation, an applicant shall submit a marketing authorisation application based on an identical dossier to the competent authority of the Member State chosen by the applicant, to prepare an assessment report on the medicinal product in accordance with Article 43(5) and to act in accordance with this Section ('reference Member State for the decentralised procedure'), and to the competent authorities in the other Member States concerned.

2. The application for marketing authorisation shall contain:

(a) the particulars and documentations referred to Articles 6, 9 to 14 and 62;

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

3. The applicant shall inform all the competent authorities of all Member States of its application at the time of submission. The competent authority of a Member State may request for justified public health reasons to enter the procedure and shall inform the applicant and the competent authority of the reference Member State for the decentralised procedure of its request within 30 days from the date of submission of the application. The applicant shall provide the competent authorities of those Member States entering the procedure with the application without undue delay.

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

   The competent authority of the reference Member State for the decentralised procedure shall summarise the deficiencies in writing. On this basis, the competent authority of the reference Member State for the decentralised procedure shall inform the applicant and the competent authorities of the Member States concerned accordingly and set a time limit to address the deficiencies. The application shall be suspended until the applicant addresses the deficiencies. If the applicant fails to address those deficiencies within the time limit set by the competent authority of the reference Member State for the decentralised procedure, the application shall be considered as withdrawn.

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

5. Within 120 days after validation of the application, the competent authority of the reference Member State for the decentralised procedure shall prepare an assessment report, a summary of product characteristics, the labelling and the package leaflet and shall send them to the Member States concerned and to the applicant.

6. Within 60 days of receipt of the assessment report, the competent authorities of the Member States concerned shall approve the assessment report, the summary of product characteristics and the labelling and package leaflet and shall inform the competent authority of the reference Member State for the decentralised procedure accordingly. The competent authority of the reference Member State for the decentralised procedure shall record the agreement of all parties, close the procedure and inform the applicant accordingly.

7. Within 30 days after acknowledgement of the agreement, the competent authorities of all Member States concerned in which an application has been submitted in accordance with paragraph 1 shall adopt a decision according to Articles 43 to 45 and in conformity with the approved assessment report, the summary of product characteristics and the labelling and package leaflet as approved.

SECTION 4

MUTUAL RECOGNITION OF NATIONAL MARKETING AUTHORISATIONS

Article 35

Scope of mutual recognition procedure for national marketing authorisations

An application for marketing authorisation for mutual recognition procedure for national marketing authorisation, granted under Articles 43 to 45 and in accordance with Article 32, shall be submitted to the competent authorities of other Member States in accordance with the procedure laid down in Article 36.

Article 36

Mutual recognition procedure for national marketing authorisations

1. An application for mutual recognition of a marketing authorisation, granted under Articles 43 to 45 and in accordance with Article 32, in several Member States in respect of the same medicinal product shall be submitted to the competent authority of the Member State that granted the marketing authorisation ('reference Member State for the mutual recognition procedure') and to the competent authorities of the Member States concerned where the applicant seeks to obtain a national marketing authorisation.

2. Application shall include a list of Member States concerned by the application.

3. The competent authority of the reference Member State for the mutual recognition procedure shall reject an application for mutual recognition of marketing authorisation of medicinal product within a year from the granting of that marketing authorisation, unless the competent authority of the Member State informs the competent authority of the reference Member State for the mutual recognition procedure of its interest in this medicinal product.

4. The applicant shall inform the competent authorities of all Member States of its application at the time of submission. The competent authority of a Member State may request for justified public health reasons to enter the procedure and shall inform the applicant and the competent authority of the reference Member State for the mutual recognition procedure of its request within 30 days from the date of submission of the application. The applicant shall provide the competent authorities of those Member States entering the procedure with the application without undue delay.

5. If the competent authorities of the Member States concerned so require, the marketing authorisation holder shall request the competent authority of the reference Member State for the mutual recognition procedure to update the assessment report drawn on the

medicinal concerned by the application. In that case, the reference Member State shall update the assessment report within 90 days after validation of the application. If the competent authorities of the Member States concerned do not require the update of the assessment report, the reference Member State shall provide the assessment report within 30 days.

6. Within 60 days of receipt of the assessment report, the competent authorities of the Member States concerned shall approve the assessment report, the summary of product characteristics, the labelling and package leaflet and shall inform the competent authority of the reference Member State accordingly.

7. The competent authority of reference Member State for the mutual recognition procedure shall record the agreement of all parties, close the procedure and inform the applicant accordingly. The assessment report together with the summary of product characteristics, labelling and package leaflet approved by the competent authority of the reference Member State for the mutual recognition procedure shall be sent to the Member States concerned and to the applicant.

8. Within 30 days after acknowledgement of the agreement, the competent authorities of all Member States concerned in which an application has been submitted in accordance with paragraph 1 shall adopt a decision according to Articles 43 to 45 in conformity with the approved assessment report, the summary of product characteristics, the labelling and package leaflet as approved.

SECTION 5

COORDINATION OF NATIONAL MARKETING AUTHORISATION

Article 37

Coordination group for decentralised and mutual recognition procedures

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

   (a) the examination of any question relating to a national marketing authorisation of a medicinal product in two or more Member States in accordance with the procedures laid down in Sections 3, 4 and 5 of this Chapter, and Article 95;

   (b) the examination of questions related to the pharmacovigilance of medicinal products covered by national marketing authorisations, in accordance with Articles 108, 110, 112, 116 and 121;

   (c) the examination of questions relating to variations of national marketing authorisations, in accordance with Article 93(1).

   For the fulfilment of its pharmacovigilance tasks contemplated under first subparagraph, point (b), including approving risk management systems and monitoring their effectiveness, the coordination group shall rely on the scientific assessment and the recommendations of the Pharmacovigilance Risk Assessment Committee referred to in Article 149 of [revised Regulation (EC) No 726/2004].

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

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

Article 147 of [revised Regulation (EC) No 726/2004] shall apply to the coordination group as regards transparency and the independence of its members.

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

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

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

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

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

Article 38

Divergent positions of Member States in decentralised or mutual recognition procedure

1. If, at the end of the period laid down in Articles 34(6) or 36(6), there is disagreement between Member States on whether the marketing authorisation can be issued, on the grounds of potential serious risk to public health, the disagreeing Member State concerned shall give a detailed explanation of the points of disagreement and the reasons for its position to the reference Member State, to the other Member States concerned and to the applicant. The points of disagreement shall be referred to the coordination group without undue delay.

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

3. Within the coordination group, all disagreeing Member States concerned shall use their best endeavours to reach agreement on the action to be taken. They shall allow the applicant the opportunity to make its point of view known orally or in writing. If, within 60 days of the communication of the points of disagreement, the Member States reach an

agreement by consensus, the reference Member State shall record the agreement, close the procedure and inform the applicant accordingly. The procedure laid down in Articles 34(7) or 36(8) shall apply.

4. If within the 60-day period laid down in paragraph 3, an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission, which shall apply the procedure laid down in Articles 41 and 42.

5. In the circumstances referred to in paragraph 4, Member States that have approved the assessment report, the summary of product characteristics, the labelling and package leaflet of the reference Member State may, at the request of the applicant, authorise the medicinal product without waiting for the outcome of the procedure laid down in Article 41. In that event, the national marketing authorisation granted shall be without prejudice to the outcome of that procedure.

Article 39

Referral procedure of divergent decisions of Member States

If applications for a national marketing authorisation have been submitted in accordance with Articles 6 and 9 to 14 for a particular medicinal product, and if Member States have adopted divergent decisions concerning the national marketing authorisation, its variation, suspension or revocation or the summary of product characteristics, the competent authority of the Member State, the Commission or the marketing authorisation holder may refer the matter to the Committee for Medicinal Products for Human Use for the application of the procedure laid down in Articles 41 and 42.

Article 40

Harmonisation of summary of product characteristics

1. In order to promote the harmonisation of national marketing authorisations for medicinal products throughout the Union, the competent authorities of the Member States shall, each year, forward to the coordination group referred to in Article 37 a list of medicinal products for which a harmonised summary of product characteristics is to be drawn up.

2. The coordination group shall lay down a list of medicinal products for which a harmonised summary of product characteristics is to be drawn up, taking into account the proposals from the competent authorities of all Member States, and shall forward that list to the Commission.

3. The Commission or the competent authority of a Member State, in agreement with the Agency and taking into account the views of interested parties, may refer the matter concerning the harmonisation of summary of products characteristics of those medicinal products to the Committee for Medicinal Products for Human Use for the application of the procedure laid down in Articles 41 and 42.

Article 41

Scientific evaluation by the Committee for Medicinal Products for Human Use in a referral procedure

1. When reference is made to the procedure laid down in this Article, the Committee for Medicinal Products for Human Use referred to in Article 148 of [revised Regulation (EC) No 726/2004] shall consider the matter concerned and shall issue a reasoned opinion within 60 days from the date when the matter was referred to it.

   However, in cases submitted to the Committee for Medicinal Products for Human Use in accordance with Articles 39, 40 and 95, this period may be extended by the Committee for Medicinal Products for Human Use for a further period of up to 90 days.

   On a proposal from its chairperson, the Committee for Medicinal Products for Human Use may agree to a shorter deadline.

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

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

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

   If necessary, the Committee for Medicinal Products for Human Use may call upon any other person to provide information relating to the matter before it or consider a public hearing.

   The Agency shall, in consultation with the parties concerned, draw up Rules of Procedure on the organisation and conduct of public hearings, in accordance with Article 163 of [revised Regulation (EC) No 726/2004].

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

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

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

(b) the summary of product characteristics proposed by the applicant or the marketing authorisation holder in accordance with Article 62 is to be amended;

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

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

(e) the medicinal product satisfies the conditions set out in Article 83 regarding medicinal products addressing an unmet medical need.

Within 12 days after receipt of the opinion, the applicant or the marketing authorisation holder may notify the Agency in writing of its intention to request a re-examination of the opinion. In that case, they shall forward to the Agency the detailed grounds for the request within 60 days after receipt of the opinion.

Within 60 days following receipt of the grounds for the request, the Committee for Medicinal Products for Human Use shall re-examine its opinion in accordance with Article 12(2), third subparagraph, of [revised Regulation (EC) No 726/2004]. The reasons for the conclusion reached further to its re-examination shall be annexed to the assessment report referred to in Article 12(2), third subparagraph, of [revised Regulation (EC) No 726/2004].

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

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

(a) a summary of product characteristics, as referred to in Article 62;

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

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

(d) the labelling and package leaflet.

Article 42

Commission decision

1. Within 12 days of receipt of the opinion of the Committee for Medicinal Products for Human Use, the Commission shall submit to the Standing Committee on Medicinal Products for Human Use referred to in Article 214(1) a draft of the decision on the application, on the basis of the requirements set out in this Directive.

In duly justified cases, the Commission may return the opinion to the Agency for further consideration.

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

Where a 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 competent authorities of the Member States and the applicant or the marketing authorisation holder.

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

Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 214(2) and (3).

3. Where a Member State raises important new questions of a scientific or technical nature that have not been addressed in the opinion delivered by the Agency, 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 decision referred to in paragraph 2 shall be addressed to all Member States and forwarded for information to the applicant or the marketing authorisation holder. The Member States concerned and the reference Member State shall adopt a decision to either grant or revoke the marketing authorisation, or vary its terms as necessary to comply with the decision referred to in paragraph 2 within 30 days following its notification. In the decision to grant, suspend, revoke or vary the marketing authorisation, the Member States shall refer to the decision adopted pursuant to paragraph 2. They shall inform the Agency accordingly.

5. Where the scope of the procedure initiated under Article 95 includes medicinal products covered by centralised marketing authorisation pursuant to Article 95(2), third subparagraph, the Commission shall, where necessary, adopt decisions to vary, suspend or revoke the marketing authorisations or to refuse the renewal of the marketing authorisations concerned in accordance with this Article.

SECTION 6

RESULTS OF EXAMINATION OF A NATIONAL MARKETING AUTHORISATION APPLICATION

Article 43

Granting of the national marketing authorisation

1. When a competent authority of the Member State grants a national marketing authorisation, it shall inform the applicant of the marketing authorisation of the summary of product characteristics, the package leaflet, the labelling as well as any conditions established in accordance with Articles 44 and 45 together with any deadlines for the fulfilment of those conditions.

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

3. The competent authorities of the Member States shall, without undue delay, make publicly available the national marketing authorisation together with the summary of product characteristics, the package leaflet as well as any conditions established in accordance with Articles 44, 45 and any obligations imposed subsequently in accordance with Article 87, together with any deadlines for the fulfilment of those conditions and obligations for each medicinal product that they have authorised.

4. The competent authority of the Member State may consider and decide upon additional evidence available, independently from the data submitted by the marketing authorisation holder. On that basis, the summary of product characteristics shall be updated if the additional evidence has an impact on the benefit-risk balance of a medicinal product.

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

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

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

Article 44

National marketing authorisation subject to conditions

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

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

   (b) to conduct post-authorisation safety studies;

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

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

(e) the existence of an adequate pharmacovigilance system;

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

(g) in case of medicinal products for which there is substantial 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;

(h) to conduct post-authorisation environmental risk assessment studies, collection of monitoring data or information on use, where identified or potential concerns about risks to the environment or public health, including antimicrobial resistance need to be further investigated after the medicinal product has been marketed;

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

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

An obligation to conduct post authorisation efficacy studies referred to in the first subparagraph, point (f), shall be based on the delegated acts adopted pursuant to Article 88.

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

Article 45

National marketing authorisation under exceptional circumstances

1. In exceptional circumstances where, in an application under Article 6 for a marketing authorisation of a medical product, or in an application under Article 92 for a new therapeutic indication of an existing marketing authorisation, an applicant is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, the competent authority of the Member State may, by derogation to Article 6, grant an authorisation under Article 43, subject to specific conditions, where the following requirements are met:

(a) the applicant has demonstrated, in the application file, that there are objective and verifiable reasons not to be able to submit comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use based on one of the grounds set out in Annex II;

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

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

2. The maintenance of the authorised new therapeutic indication and the validity of the national marketing authorisation shall be linked to the reassessment of the conditions set out in paragraph 1 after 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 competent authorities of the Member State and specified in the marketing authorisation.

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

Article 46

Validity and renewal of marketing authorisation

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

By way of derogation from the first subparagraph, a national marketing authorisation granted in accordance with Article 45(1) shall be valid for five years and be subject to renewal in accordance with paragraph 2.

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

2. The marketing authorisation holder may submit an application for a renewal of a national marketing authorisation granted under paragraph 1, second or third subparagraph. Such application shall be submitted at least nine months before the national marketing authorisation ceases to be valid.

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

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

Article 47

Refusal of a national marketing authorisation

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

   (a) the benefit-risk balance is not considered to be favourable;

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

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

   (d) the 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) the labelling and package leaflet proposed by the applicant are not in accordance with Chapter VI.

2. The national marketing authorisation shall also be refused if any particulars or documentations submitted in support of the application do not comply with Article 6, paragraphs 1 to 6, and Articles 9 to 14.

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

SECTION 7

SPECIFIC REQUIREMENTS FOR PAEDIATRIC MEDICINAL PRODUCTS

Article 48

Compliance with the paediatric investigation plan

1. The competent authority of the Member State for which an application for marketing authorisation or variation of a marketing authorisation is submitted under the provisions of this Chapter or of the Chapter VIII, shall verify whether it complies with the requirements laid down in Article 6(5).

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

3. The Committee for Medicinal Products for Human Use, as referred to in Article 148 of [revised Regulation (EC) No 726/2004] may, in the following cases, be requested to give its opinion as to whether studies conducted by the applicant are in compliance with the agreed paediatric investigation plan as defined in Article 74 of [revised Regulation (EC) No 726/2004]:

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

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

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

5. Member States shall take due account of an opinion drawn up in accordance with paragraph 3.

6. When the competent authority of the Member State, during the scientific assessment of a valid application for a marketing authorisation or a variation of a marketing authorisation, concludes that the studies are not in conformity with the agreed paediatric investigation plan, the medicinal product shall not be eligible for the rewards and incentives provided for in Article 86.

Article 49

Data deriving from a paediatric investigation plan

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

(a) the results of all clinical studies, conducted in compliance with an agreed paediatric investigation plan as referred to in Article 6(5), point (a), shall be included in the summary of product characteristics and, if appropriate, in the package leaflet, or

(b) any agreed waiver as referred to in Article 6(5), points (b) and (c), shall be recorded in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.

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

3. An application for new therapeutic indications, including paediatric indications, new pharmaceutical forms, new strengths and new routes of administration of medicinal products authorised in accordance with the provisions under this Chapter or of the provisions under Chapter VIII and which are protected either by a supplementary protection certificate under [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate, may be submitted under the procedure laid down in Articles 41 and 42.

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

Chapter IV
Prescription status

Article 50

Prescription status of medicinal products

1. When a marketing authorisation is granted, the competent authorities shall, by applying the criteria laid down in Article 51, specify the prescription status of the medicinal product as:

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

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

2. The competent authorities may fix sub-categories for medicinal products that are subject to medical prescription. In that case, they shall specify the following prescription status:

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

   (b) medicinal products subject to special medical prescription;

   (c) medicinal products on 'restricted' medical prescription, reserved for use in certain specialised areas.

Article 51

Medicinal products subject to medical prescription

1. A medicinal product shall be subject to medical prescription where it:

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

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

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

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

   (e) is an antimicrobial; or

   (f) contains an active substance which are persistent, bioaccumulative and toxic, or very persistent and very bioaccumulative, or persistent, mobile and toxic, or very persistent and very mobile for which medical prescription is required as risk

minimisation measure with regard to the environment, unless the use of the medicinal product and the patient safety require otherwise.

2. Member States may set additional conditions on the prescription of antimicrobials, restrict the validity of medical prescription and limit the quantities prescribed to the amount required for the treatment or therapy concerned or submitting certain antimicrobial medicinal products to special medical prescription or restricted prescription.

3. Where Member States provide for the sub-category of medicinal products subject to special medical prescription, they shall take account of the following factors:

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

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

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

4. Where Member States provide for the sub-category of medicinal products subject to restricted prescription, they shall take account of the following factors:

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

   (b) the medicinal product is used in the treatment of conditions that must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere;

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

5. A competent authority may waive application of the paragraphs 1, 3 and 4 having regard to:

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

   (b) other circumstances of use that it has specified.

6. If a competent authority does not designate medicinal products into sub-categories referred to in Article 50(2), it shall nevertheless take into account the criteria laid down in paragraphs 3 and 4 in determining whether any medicinal product shall be classified as a medicinal product subject to medical prescription.

Article 52

Medicinal products not subject to medical prescription

Medicinal products not subject to medical prescription shall be those that do not meet the criteria laid down in Article 51.

Article 53

List of medicinal products subject to medical prescription

The competent authorities shall draw up a list of the medicinal products subject, on their territory, to medical prescription, specifying, if necessary, the category of prescription status. They shall update this list annually.

Article 54

Amendment of prescription status

When new facts are brought to their attention, the competent authorities shall examine and, as appropriate, amend the prescription status of a medicinal product by applying the criteria listed in Article 51.

Article 55

Data protection of evidence for the change of prescription status

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

Chapter V
Obligations and liability of the marketing authorisation holder

Article 56

General obligations

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

2. The marketing authorisation holder of a medicinal product placed on the market in a Member State shall notify the competent authority of the Member State concerned of the

date of actual placing on the market of the medicinal product in that Member State, taking into account the various presentations authorised.

3. The marketing authorisation holder of a medicinal product placed on the market in a Member State shall, within the limits of its responsibility, ensure appropriate and continued supplies of that medicinal product to wholesale distributors, pharmacies or persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered.

   The arrangements for implementing the first subparagraph should, moreover, be justified on grounds of public health protection and be proportionate in relation to the objective of such protection, in compliance with the Treaty rules, particularly those concerning the free movement of goods and competition.

4. The marketing authorisation holder shall, at all stages of manufacturing and distribution ensure that the starting materials and ingredients of the medicinal products and the medicinal products themselves comply with the requirements of this Directive and, where relevant, the [revised Regulation (EC) No 726/2004] and other Union law and shall verify that such requirements are met.

5. For integral combination of a medicinal product with a medical device and for combinations of a medicinal product with a product other than a medical device, the marketing authorisation holder shall be responsible for the whole product in terms of compliance of the medicinal product with the requirements of this Directive and the [revised Regulation (EC) No 726/2004].

6. The marketing authorisation holder shall be established in the Union.

7. Where the marketing authorisation holder considers or has reason to believe that the medicinal product it has made available on the market is not in conformity with the marketing authorisation or this Directive and the [revised Regulation (EC) No 726/2004] it shall immediately take the necessary corrective actions to bring that medicinal product into conformity, to withdraw it or recall it, as appropriate. The marketing authorisation holder shall immediately inform the competent authorities and the distributors concerned to that effect.

8. Upon request, the marketing authorisation holder shall provide the competent authorities with free samples in sufficient quantities to enable controls to be made on the medicinal products that it has placed on the market.

9. Upon request the marketing authorisation holder shall provide the competent authority with all data relating to the volume of sales of the medicinal product, and any data in its possession relating to the volume of prescriptions.

Article 57

Responsibility to report on public financial support

1. The marketing authorisation holder shall declare to the public any direct financial support received from any public authority or publicly funded body, in relation to any activities for the research and development of the medicinal product covered by a national or a

centralised marketing authorisation, irrespective of the legal entity that received that support.

2. Within 30 days after the marketing authorisation is granted the marketing authorisation holder shall:

   (a) draw up an electronic report listing:

      (i) the amount of financial support received and the date thereof;

      (ii) the public authority or publicly funded body that provided the financial support referred to in point (i);

      (iii) the legal entity that received the support referred to in point (i).

   (b) ensure that the electronic report is accurate and that it has been audited by an independent external auditor;

   (c) make the electronic report accessible to the public via a dedicated webpage;

   (d) communicate the electronic link to such webpage to the competent authority of the Member State or, where appropriate, to the Agency.

3. For the medicinal products authorised under this Directive, the competent authority of the Member State shall communicate in a timely manner the electronic link to the Agency.

4. The marketing authorisation holder shall keep the electronic link up to date and, as necessary, update the report annually.

5. The Member States shall take appropriate measures to ensure that paragraphs 1, 2 and 4 are complied with by the marketing authorisation holder established in their country.

6. The Commission may adopt implementing acts to lay down the principles and format for the information to be reported pursuant to paragraph 2. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 214(2).

Article 58

Traceability of substances used in the manufacture of medicinal products

1. The marketing authorisation holder shall, when necessary, ensure the traceability of an active substance, starting material, excipient or any other substance intended or expected to be present in a medicinal product at all stages of manufacturing and distribution.

2. The marketing authorisation holder shall be able to identify any natural or legal person from whom they have been supplied with an active substance, starting material, excipient or any other substance intended or expected to be present in a medicinal product.

3. The marketing authorisation holder and its suppliers of an active substance, starting material, excipient or any other substance used in the manufacturing of a medicinal product shall have in place systems and procedures that allow for the information referred to in paragraph 2 to be made available, upon request, to the competent authorities.

4. The marketing authorisation holder and its suppliers shall have in place systems and procedures to identify the other natural or legal persons to whom products referred to in paragraph 2 have been supplied. This information shall, upon request, be made available to the competent authorities.

Article 59

Placing on the market of products with paediatric indications

Where medicinal products are authorised for a paediatric indication following completion of an agreed paediatric investigation plan and those medicinal products have already been marketed with other therapeutic indications, the marketing authorisation holder shall, within two years of the date on which the paediatric indication is authorised, place the medicinal product on the market taking into account the paediatric indication in all Member States where the medicinal product is already placed on the market.

A register, coordinated by the Agency, and made publicly available, shall mention these deadlines.

Article 60

Discontinuation of the placing on the market of paediatric products

If a medicinal product is authorised for a paediatric indication and the marketing authorisation holder has benefited from rewards or incentives under Article 86 of this Directive or Article 93 of [revised Regulation (EC) No 726/2004], and these periods of protection have expired, and if the marketing authorisation holder intends to discontinue placing the medicinal product on the market, the marketing authorisation holder shall transfer the marketing authorisation to a third party or allow a third party, which has declared its intention to continue to place the medicinal product in question on the market, to use the pharmaceutical, non-clinical and clinical documentation contained in the file of the medicinal product on the basis of Article 14.

The marketing authorisation holder shall inform the competent authorities of its intention to discontinue the placing on the market of the medicinal product no less than twelve months before the discontinuation. The competent authorities shall make this fact publicly available.

Article 61

Liability of the marketing authorisation holder

The marketing authorisation shall not affect the civil and criminal liability of the marketing authorisation holder.

Chapter VI
Product information and labelling

Article 62

Summary of product characteristics

1. The summary of product characteristics shall contain the particulars listed in Annex V.

2. For marketing authorisations under Articles 9 and 11 and subsequent variations to such marketing authorisations, if one or more of the therapeutic indications, posologies, pharmaceutical forms, methods or routes of administration or any other way in which the medicinal product may be used are still covered by patent law or a supplementary protection certificate for medicinal products at the time when the generic or biosimilar medicinal product was marketed, the applicant for an authorisation for a generic or biosimilar medicinal product may request not to include this information in their marketing authorisation.

3. For all medicinal products, a standard text shall be included in the summary of product characteristics expressly asking healthcare professionals to report any suspected adverse reaction in accordance with the national reporting system referred to in Article 106(1). Different ways of reporting, including electronic reporting, shall be available in compliance with Article 106(1), second subparagraph.

Article 63

General principles on package leaflet

1. A package leaflet shall be mandatory for medicinal products.

2. The package leaflet shall be written and designed in a clear and understandable way, enabling users to act appropriately, when necessary with the help of healthcare professionals.

3. Member States may decide that the package leaflet shall be made available in paper format or electronically, or both. In the absence of such specific rules in a Member State, a package leaflet in paper format shall be included in the packaging of a medicinal product. If the package leaflet is only made available electronically, the patient's right to a printed copy of the package leaflet should be guaranteed upon request and free of charge and it should be ensured that the information in digital format is easily accessible to all patients.

4. By derogation from paragraphs 1 and 2, where the information required under Articles 64 and 73 is directly conveyed on the outer packaging or on the immediate packaging, a package leaflet shall not be required.

5. The Commission is empowered to adopt delegated acts in accordance with Article 215 to amend paragraph 3 by making mandatory the electronic version of the package leaflet. That delegated act shall also establish the patient's right to a printed copy of the package leaflet upon request and free of charge. The delegation of powers shall apply as of [OP

please insert the date = five years following 18 months after the date of entering into force of this Directive].

6. The Commission shall adopt implementing acts in accordance with the examination procedure referred to in Article 214(2) to establish common standards for the electronic version of the package leaflet, the summary of product characteristics and the labelling, taking into account available technologies.

7. Where the package leaflet is made available electronically, the individual right to privacy shall be ensured. Any technology giving access to the information shall not allow the identification or tracking of individuals, nor shall it be used for commercial purposes.

Article 64

Content of package leaflet

1. The package leaflet shall be drawn up in accordance with the summary of product characteristics, referred to in Article 62(1) and shall include the particulars listed in Annex VI.

2. For all medicinal products, a standardised text shall be included, expressly asking patients to communicate any suspected adverse reaction to their doctor, pharmacist, healthcare professional or directly to the national reporting system referred to in Article 106(1), and specifying the different ways of reporting available (electronic reporting, postal address or others) in compliance with Article 106(1), second subparagraph.

3. The package leaflet shall reflect the results of consultations with target patient groups to ensure that it is legible, clear and easy to use.

Article 65

Content of labelling particulars

1. The outer packaging of medicinal products or, where there is no outer packaging, the immediate packaging, with the exception of the packaging referred to in Article 66, paragraphs 2 and 3, shall include the labelling particulars listed in Annex IV.

2. The Commission is empowered to adopt delegated acts in accordance with Article 215 to:

   (a) amend the list of labelling particulars set out in Annex IV in order to take account of scientific progress or patient needs;

   (b) supplement Annex IV by setting out a reduced list of mandatory labelling particulars that shall appear on the outer packaging of multi-language packages.

Article 66

Labelling of blister packs or small immediate packaging

1. The particulars laid down in Annex IV shall appear on immediate packagings other than those referred to in the paragraphs 2 and 3.

2. The following particulars at least shall appear on immediate packagings that take the form of blister packs and are placed in an outer packaging that complies with the requirements laid down in Articles 65 and 73.

   (a) the name of the medicinal product;

   (b) the name of the marketing authorisation holder placing the product on the market;

   (c) the expiry date;

   (d) the batch number.

3. The following particulars at least shall appear on small immediate packaging units on which the particulars laid down in Articles 65 and 73 cannot be displayed, shall include at least the following labelling particulars:

   (a) the name of the medicinal product and, if necessary, the route of administration;

   (b) the method of administration;

   (c) the expiry date;

   (d) the batch number;

   (e) the contents by weight, by volume or by unit.

Article 67

Safety features

1. Medicinal products subject to prescription shall bear the safety features referred to in Annex IV, unless they have been listed in accordance with the procedure referred to in paragraph 2, second subparagraph, point (b).

   Medicinal products not subject to prescription shall not bear the safety features referred to in Annex IV, unless, by way of exception, they have been listed in accordance with the procedure referred to in paragraph 2, second subparagraph, point (b).

2. The Commission shall adopt delegated acts in accordance with Article 215 to supplement Annex IV by laying down detailed rules for the safety features.

   Those delegated acts shall set out:

   (a) the characteristics and technical specifications of the unique identifier of the safety features referred to in Annex IV that enables the authenticity of medicinal products to be verified and individual packs to be identified;

   (b) the lists containing the medicinal products or product categories that, in the case of medicinal products subject to prescription shall not bear the safety features, and in

the case of medicinal products not subject to prescription shall bear the safety features referred to in Annex IV;

(c) the procedures for the notification to the Commission provided for in paragraph 4 and a rapid system for evaluating and deciding on such notification for the purpose of applying point (b);

(d) the modalities for the verification of the safety features referred to in Annex IV by the manufacturers, wholesale distributors, pharmacists and natural or legal persons authorised or entitled to supply medicinal products to the public and by the competent authorities;

(e) provisions on the establishment, management and accessibility of the repositories system in which information on the safety features, enabling the verification of the authenticity and identification of medicinal products, as provided for in Annex IV, shall be contained.

The lists referred to in the second subparagraph, point (b), shall be established considering the risk of falsification relating to the medicinal products or categories of medicinal products concerned. To this end, at least the following criteria shall be applied:

(a) the price and sales volume of the medicinal product;

(b) the number and frequency of previous cases of falsified medicinal products being reported within the Union and in third countries and the evolution of the number and frequency of such cases to date;

(c) the specific characteristics of the medicinal products concerned;

(d) the severity of the conditions intended to be treated;

(e) other potential risks to public health.

The modalities referred to in the second subparagraph, point (d), shall allow the verification of the authenticity of each supplied pack of the medicinal products bearing the safety features referred to in Annex IV and determine the extent of such verification. When establishing those modalities, the particular characteristics of the supply chains in Member States, and the need to ensure that the impact of verification measures on particular actors in the supply chains is proportionate, shall be taken into account.

For the purposes of the second subparagraph, point (e), the costs of the repositories system shall be borne by the manufacturing authorisation holders of medicinal products bearing the safety features.

3. When adopting delegated acts referred to in paragraph 2, the Commission shall take due account of at least the following:

(a) the protection of personal data as provided for in Union law;

(b) the legitimate interests to protect information of a commercially confidential nature;

(c) the ownership and confidentiality of the data generated by the use of the safety features; and

(d) the cost-effectiveness of the measures.

4. The competent authorities of the Member States shall notify the Commission of non-prescription medicinal products that they judge to be at risk of falsification and may inform the Commission of medicinal products that they deem not to be at risk of falsification in accordance with the criteria set out in paragraph 2, second subparagraph, point (b).

5. Member States may, for the purposes of reimbursement or pharmacovigilance, extend the scope of application of the unique identifier referred to in Annex IV to any medicinal product subject to prescription or subject to reimbursement.

6. Member States may, for the purposes of reimbursement, pharmacovigilance, pharmacoepidemiology or for data protection prolongation for market launch use the information contained in the repositories system referred to paragraph 2, second subparagraph, point (e).

7. Member States may, for the purposes of patient safety, extend the scope of application of the anti-tampering device referred to in Annex IV to any medicinal product.

Article 68

Labelling and instruction leaflet of radionuclides and radiopharmaceuticals

1. In addition to the rules laid down in this Chapter, the outer carton and the container of medicinal products containing radionuclides shall be labelled in accordance with the regulations for the safe transport of radioactive materials laid down by the International Atomic Energy Agency. Moreover, the labelling shall comply with the provisions set out in paragraphs 2 and 3.

2. The label on the shielding shall include the particulars laid down in Article 65. In addition, the label on the shielding shall explain in full, the codings used on the vial and shall indicate, where necessary, for a given time and date, the amount of radioactivity per dose or per vial and the number of capsules, or, for liquids, the number of millilitres in the container.

3. The vial shall be labelled with the following information:

(a) the name or code of the medicinal product, including the name or chemical symbol of the radionuclide;

(b) the batch identification and expiry date;

(c) the international symbol for radioactivity;

(d) the name and address of the manufacturer;

(e) the amount of radioactivity as specified in paragraph 2.

4. The competent authority shall ensure that a detailed instruction leaflet is enclosed with the packaging of radiopharmaceuticals, radionuclide generators, radionuclide kits or radionuclide precursors. The text of this leaflet shall be established in accordance with Article 64(1). In addition, the leaflet shall include any precautions to be taken by the user

and the patient during the preparation and administration of the medicinal product and special precautions for the disposal of the packaging and its unused contents.

Article 69

Special information requirements for antimicrobials

1. The marketing authorisation holder shall ensure availability of educational material to healthcare professionals, including through medical sales representatives as referred to in Article 175(1), point (c), regarding the appropriate use of diagnostic tools, testing or other diagnostic approaches related to antimicrobial-resistant pathogens, that may inform on the use of the antimicrobial.

2. The marketing authorisation holder shall include in the packaging of antimicrobials a document that contains specific information about the medicinal product concerned and that is made available to the patient in addition to the product leaflet ("awareness card") with information on antimicrobial resistance and the appropriate use and disposal of antimicrobials.

   Member States may decide that the awareness card shall be made available in paper format or electronically, or both. In the absence of such specific rules in a Member State, an awareness card in paper format shall be included in the packaging of an antimicrobial.

3. The text of the awareness card shall be aligned with Annex VI.

Article 70

Legibility

The package leaflet and labelling particulars referred to in this Chapter shall be easily legible, clearly comprehensible and indelible.

Article 71

Accessibility for persons with disabilities

The name of the medicinal product shall also be expressed in Braille format on the packaging. The marketing authorisation holder shall ensure that the package leaflet referred to in Article 63 is made available upon request from patients' organisations in formats appropriate for persons with disabilities, including blind and partially-sighted persons.

Article 72

Member States labelling requirements

1. Notwithstanding Article 77 Member States may require the use of certain forms of labelling of the medicinal product making it possible to ascertain:

   (a) the price of the medicinal product;

(b) the reimbursement conditions of social security organisations;

(c) the legal status for supply to the patient, in accordance with Chapter IV;

(d) authenticity and identification in accordance with Article 67(5).

2. For medicinal products for which a centralised marketing authorisation as referred to in Article 5 has been granted, Member States shall, when applying this Article, observe the detailed guidance referred to in Article 77.

Article 73

Symbols and pictogram

The outer packaging and the package leaflet may include symbols or pictograms designed to clarify certain information set out in Articles 64(1) and 65 and other information compatible with the summary of product characteristics that is useful for the patient, to the exclusion of any element of a promotional nature.

Article 74

Requirements on languages

1. The particulars for labelling listed in Articles 64 and 65, shall appear in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.

2. Paragraph 1 shall not prevent those particulars from being indicated in several languages, provided that the same particulars appear in all the languages used.

3. The package leaflet must be clearly legible in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State.

4. The competent authorities of the Member State may also grant a full or partial exemption to the obligation that the labelling and the package leaflet must be in an official language or official languages of the Member State where the medicinal product is placed on the market, as specified, for the purposes of this Directive, by that Member State. For the purpose of multi-language packages, Member States may allow the use on the labelling and package leaflet of an official language of the Union that is commonly understood in the Member States where the multi-language package is marketed.

Article 75

Member States exemptions from requirements for labelling and package leaflet

The competent authorities of the Member States may, subject to measures they consider necessary to safeguard public health, grant an exemption to the obligation that the particulars required in Articles 64 and 65 should appear on the labelling and in the package leaflet in the following cases:

(a) where the medicinal product is not intended to be delivered directly to the patient;

(b) where there are problems in respect of the availability of the medicinal product;

(c) where there are space constraints due to the size of the packaging or of the package leaflet or in case of multilingual packages or package leaflets;

(d) in the context of a public health emergency;

(e) to facilitate access to medicines in Member States.

Article 76

Approval of the labelling and package leaflet information

1. One or more mock-ups of the outer packaging and the immediate packaging of a medicinal product, together with the package leaflet, shall be submitted to the competent authorities for authorising marketing when the marketing authorisation is requested. The results of assessments carried out in cooperation with target patient groups shall also be provided to the competent authority.

2. The competent authority shall refuse the marketing authorisation if the labelling or the package leaflet do not comply with the provisions of this Chapter or if they are not in accordance with the particulars listed in the summary of product characteristics.

3. All proposed changes to an aspect of the labelling or the package leaflet covered by this Chapter and not connected with the summary of product characteristics shall be submitted to the competent authorities. If the competent authorities have not opposed a proposed change within 90 days following the introduction of the request, the applicant may put the change into effect.

4. The fact that the competent authority does not refuse a marketing authorisation pursuant to paragraph 2 or a change to the labelling or the package leaflet pursuant to paragraph 3 does not alter the general legal liability of the manufacturer and the marketing authorisation holder.

Article 77

Guidance on labelling particulars

In consultation with the Member States and the parties concerned, the Commission shall draw up and publish detailed guidance concerning in particular:

(a) the wording of certain special warnings for certain categories of medicinal products;

(b) the particular information needs relating to non-prescription medicinal products;

(c) the legibility of particulars on the labelling and package leaflet;

(d) the methods for the identification and authentication of medicinal products;

(e) the list of excipients that must feature on the labelling of medicinal products and the way in which these excipients must be indicated;

(f) harmonised provisions for the implementation of Article 72.

Article 78

Placing on the market of labelled medicinal products

Member States may not prohibit or impede the placing on the market of medicinal products within their territory on grounds connected with labelling or the package leaflet where these comply with the requirements of this Chapter.

Article 79

Non-compliance with the requirements for labelling and package leaflet

Where the provisions of this Chapter are not complied with, and a notice served on the marketing authorisation holder concerned has remained without effect, the competent authorities of the Member States may suspend the marketing authorisation, until the labelling and the package leaflet of the medicinal product in question have been made to comply with the requirements of this Chapter.

Chapter VII
Regulatory protection, unmet medical needs and rewards for paediatric medicinal products

Article 80

Regulatory data and market protection

1. The data referred to in Annex I, originally submitted with the view to obtaining a marketing authorisation shall not be referred to by another applicant for a subsequent marketing authorisation during the period determined in accordance with Article 81 (‘regulatory data protection period’).

2. A medicinal product concerned by a subsequent marketing authorisation referred to in paragraph 1 shall not be placed on the market for a period of two years after the expiry of the relevant regulatory data protection periods referred to in Article 81.

3. By way of derogation from paragraph 1, the marketing authorisation holder concerned may grant the marketing authorisation applicant for another marketing authorisation a letter of access to its data submitted under Annex I, as referred to in Article 14.

4. By way of derogation from the paragraphs 1 and 2, when a compulsory licence has been granted by a relevant authority in the Union to a party to address a public health emergency, the data and market protection shall be suspended with regard to that party insofar as the compulsory licence requires, and during the duration period of the compulsory licence.

5. The data protection period set out to in paragraph 1 shall also apply in Member States where the medicinal product is not authorised or is no longer authorised.

Article 81

Regulatory data protection periods

1. The regulatory data protection period shall be six years from the date when the marketing authorisation for that medicinal product was granted in accordance with Article 6(2). For marketing authorisations that belong to the same global marketing authorisation the period of data protection shall start from the date when the initial marketing authorisation was granted in the Union.

2. Subject to a scientific evaluation by the relevant competent authority, the data protection period referred to in paragraph 1 shall be prolonged by:

   (a) 24 months, where the marketing authorisation holder demonstrates that the conditions referred to in Article 82(1) are fulfilled within two years, from the date when the marketing authorisation was granted or, within three years from that date for any of the following entities:

      (i) SMEs within the meaning of Commission Recommendation 2003/361/EC;

      (ii) entities not engaged in an economic activity ('not-for-profit entity'); and

      (iii) undertakings that, by the time of granting of a marketing authorisation, have received not more than five centralised marketing authorisations for the undertaking concerned or, in the case of an undertaking belonging to a group, for the group of which it is part, since the establishment of the undertaking or the group, whichever is earliest.

   (b) six months, where the marketing authorisation applicant demonstrates at the time of the initial marketing authorisation application that the medicinal product addresses an unmet medical need as referred to in Article 83;

   (c) six months, for medicinal products containing a new active substance, where the clinical trials supporting the initial marketing authorisation application use a relevant and evidence-based comparator in accordance with scientific advice provided by the Agency;

   (d) 12 months, where the marketing authorisation holder obtains, during the data protection period, an authorisation for an additional therapeutic indication for which the marketing authorisation holder has demonstrated, with supporting data, a significant clinical benefit in comparison with existing therapies.

In the case of a conditional marketing authorisation granted in accordance with Article 19 of [revised Regulation (EC) No 726/2004] the prolongation referred to in the first subparagraph, point (b), shall only apply if, within four years of the granting of the conditional marketing authorisation, the medicinal product has been granted a marketing authorisation in accordance with Article 19(7) of [revised Regulation (EC) No 726/2004.

The prolongation referred to in the first subparagraph, point (d), may only be granted once.

3. The Agency shall set the scientific guidelines referred to in paragraph 2, point (c), on criteria for proposing a comparator for a clinical trial, taking into account the results of the consultation of the Commission and the authorities or bodies involved in the mechanism of consultation referred to in Article 162 of [revised Regulation (EC) No 726/2004].

Article 82

Prolongation of the data protection period for medicinal products supplied in Member States

1. The prolongation of the data protection period referred to in Article 81(2), first subparagraph, point (a), shall only be granted to medicinal products if they are released and continuously supplied into the supply chain in a sufficient quantity and in the presentations necessary to cover the needs of the patients in the Member States in which the marketing authorisation is valid.

   The prolongation referred to in the first subparagraph shall apply to medicinal products that have been granted a centralised marketing authorisation, as referred to in Article 5 or that have been granted a national marketing authorisation through the decentralised procedure, as referred to in Chapter III, Section 3.

2. To receive a prolongation referred to in Article 81(2), first subparagraph, point (a), the marketing authorisation holder shall apply for a variation of the relevant marketing authorisation.

   The application for a variation shall be submitted between 34 and 36 months after the date when the initial marketing authorisation was granted, or for entities referred to in Article 81(2), first subparagraph, point (a), between 46 and 48 months, after that date.

   The application for a variation shall contain documentation from the Member States in which the marketing authorisation is valid. Such documentation shall:

   (a) confirm that the conditions set out in paragraph 1 have been satisfied in their territory; or

   (b) waive the conditions set out in paragraph 1 in their territory for the purpose of the prolongation.

Positive decisions adopted in accordance with Articles 2 and 6 of Council Directive 89/105/EEC[37] shall be considered equivalent to a confirmation referred to in the third subparagraph, point (a).

3. To receive the documentation referred to in paragraph 2, third subparagraph, the marketing authorisation holder shall make a request to the relevant Member State. Within 60 days from the request of the marketing authorisation holder, the Member State shall issue a confirmation of compliance or, a reasoned statement of non-compliance or alternatively provide a statement of non-objection to prolong the period of regulatory data protection pursuant to this Article.

4. In cases where a Member State has not replied to the application of the marketing authorisation holder within the deadline referred to in paragraph 3, it shall be considered that a statement of non-objection has been provided.

For medicinal products granted a centralised marketing authorisation the Commission shall vary the marketing authorisation pursuant to Article 47 of [revised Regulation (EC) No 726/2004] to prolong the data protection period. For medicinal products granted a marketing authorisation in accordance with the decentralised procedure, the competent authorities of the Member States shall vary the marketing authorisation pursuant to Article 92 to prolong the data protection period**.**

5. Member States representatives may request the Commission to discuss issues related to the practical application of this Article in the Committee established by Council Decision 75/320/EEC[38] ('Pharmaceutical Committee'). The Commission may invite bodies responsible for health technology assessment as referred to in Regulation (EU) 2021/2282 or national bodies responsible for pricing and reimbursement, as required, to participate in the deliberations of the Pharmaceutical Committee.

6. The Commission, based on the experience of Member States and relevant stakeholders, may adopt implementing measures relating to the procedural aspects outlined in this Article and regarding the conditions mentioned in paragraph 1. Those implementing acts shall be adopted in accordance with the procedure referred to in Article 214(2).

Article 83

Medicinal products addressing an unmet medical need

1. A medicinal product shall be considered as addressing an unmet medical need if at least one of its therapeutic indications relates to a life threatening or severely debilitating disease and the following conditions are met:

   (a) there is no medicinal product authorised in the Union for such disease, or, where despite medicinal products being authorised for such disease in the Union, the disease is associated with a remaining high morbidity or mortality;

[37] 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).

[38] Council Decision of 20 May 1975 setting up a pharmaceutical committee (OJ L 147, 9.6.1975, p. 23).

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

2. Designated orphan medicinal products referred to in Article 67 of [revised Regulation (EC) No 726/2004] shall be considered as addressing an unmet medical need.

3. Where 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 of [revised Regulation (EC) No 726/2004].

Article 84

Data protection for repurposed medicinal products

1. A regulatory data protection period of four years shall be granted for a medicinal product with respect to a new therapeutic indication not previously authorised in the Union, provided that:

(a) adequate non-clinical or clinical studies were carried out in relation to the therapeutic indication demonstrating that it is of significant clinical benefit, and

(b) the medicinal product is authorised in accordance with Articles 9 to 12 and has not previously benefitted from data protection, or 25 years have passed since the granting of the initial marketing authorisation of the medicinal product concerned.

2. The data protection period referred to in paragraph 1 may only be granted once for any given medicinal product.

3. During the data protection period referred to in paragraph 1, the marketing authorisation shall indicate that the medicinal product is an existing medicinal product authorised in the Union that has been authorised with an additional therapeutic indication.

Article 85

Exemption to the protection of intellectual property rights

Patent rights, or supplementary protection certificates under the [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted] shall not be regarded as infringed when a reference medicinal product is used for the purposes of:

(a) studies, trials and other activities conducted to generate data for an application, for:

(i) a marketing authorisation of generic, biosimilar, hybrid or bio-hybrid medicinal products and for subsequent variations;

(ii) health technology assessment as defined in Regulation (EU) 2021/2282;

(iii) pricing and reimbursement.

(b) the activities conducted exclusively for the purposes set out in point (a), may cover the submission of the application for a marketing authorisation and the offer, manufacture,

sale, supply, storage, import, use and purchase of patented medicinal products or processes, including by third party suppliers and service providers.

This exception shall not cover the placing on the market of the medicinal products resulting from such activities.

Article 86

Rewards for paediatric medicinal products

1. Where an application for marketing authorisation, includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the holder of the patent or supplementary protection certificate shall be entitled to a six-month extension of the period referred to in Article 13, paragraphs 1 and 2 of [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted].

   The first subparagraph shall also apply where completion of the agreed paediatric investigation plan fails to lead to the authorisation of a paediatric indication, but the results of the studies conducted are reflected in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product concerned.

2. The inclusion in a marketing authorisation of the statement referred to in Article 49(2) of this Directive or in Article 90(2) of [revised Regulation (EC) No 726/2004] shall be used for the purposes of applying paragraph 1.

3. Where the procedures laid down in Chapter III, Sections 3 and 4, have been used, the six-month extension of the period referred to in paragraph 1 shall be granted only if the product is authorised in all Member States.

4. In the case of an application for new therapeutic indications, including paediatric indications, new pharmaceutical forms, new strengths and new routes of administration of authorised medicinal products which are protected either by a supplementary protection certificate under [Regulation (EC) No 469/2009 - OP please replace reference by new instrument when adopted], or by a patent which qualifies for the granting of the supplementary protection certificate which leads to the authorisation of a new paediatric indication, paragraphs 1, 2 and 3 shall not apply if the applicant applies for, and obtains, a one-year extension of the period of marketing protection for the medicinal product concerned, on the grounds that this new paediatric indication brings a significant clinical benefit in comparison with existing therapies, in accordance with Article 81(2), first subparagraph, point (d).

Chapter VIII
Post-marketing authorisation measures

Article 87

Imposed post-authorisation studies

1. After the granting of a marketing authorisation, the competent authority of the Member State may impose an obligation on the marketing authorisation holder:

   (a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. If the same concerns apply to more than one medicinal product, the competent authority of the Member State shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorisation holders concerned to conduct a joint post-authorisation safety study;

   (b) to conduct a post-authorisation efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorisation efficacy study shall be based on the delegated acts adopted pursuant to Article 88 while taking into account the scientific guidance referred to in Article 123.

   (c) to conduct a post-authorisation environmental risk assessment study, collection of monitoring data or information on use, if there are concerns about the risks to the environment or public health, including antimicrobial resistance, due to an authorised medicinal product, or related active substance.

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

   The imposition of such an obligation shall be duly justified, notified in writing, and shall include the objectives and timeframe for submission and conduct of the study.

2. The competent authority of the Member State shall provide the marketing authorisation holder with an opportunity to present written observations in response to the imposition of the obligation within a time limit which it shall specify, if the marketing authorisation holder so requests within 30 days of receipt of the written notification of the obligation.

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

Article 88

Delegated acts on post-authorisation efficacy studies

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

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

Article 89

Recording of conditions related to marketing authorisations

1. The marketing authorisation holder shall incorporate any safety or efficacy conditions referred to in Articles 44, 45 and 87 in the risk management system.

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

Article 90

Update of marketing authorisation related to scientific and technological progress

1. After a marketing authorisation has been granted in accordance with Chapter III, the marketing authorisation holder shall, in respect of the methods of manufacture and control stated in the application for that marketing authorisation, take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and controlled by means of generally accepted scientific methods.

   Those changes shall be subject to the approval of the competent authority of the Member State concerned.

2. The marketing authorisation holder shall without undue delay provide the competent authority of the Member State with any new information that might entail the amendment of the particulars or documentations referred to in Articles 6, 9 to 13, 62, 41(5), Annex I or Annex II.

   In particular, the marketing authorisation holder shall without undue delay inform the competent authority of the Member State of any prohibition or restriction imposed on the marketing authorisation holder or any entity in contractual relationship with the marketing authorisation holder by the competent authorities of any country in which the medicinal product is marketed and of any other new information that might influence the evaluation of the benefits and risks of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all therapeutic indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorisation.

3. The marketing authorisation holder shall ensure that the terms of the marketing authorisation including the summary of product characteristics, the labelling and package leaflet are kept up to date with current scientific knowledge, including the conclusions of the assessment and recommendations made publicly available by means of the European medicines web-portal set up in accordance with Article 104 of [revised Regulation (EC) No 726/2004].

4. The competent authority of the Member State may at any time request the marketing authorisation holder to submit data demonstrating that the benefit-risk balance remains favourable. The marketing authorisation holder shall answer fully and within the time limit

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

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

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

Article 91

Update of risk management plans

1. The marketing authorisation holder of a medicinal product referred to in Articles 9 and 11 shall submit to the competent authorities of the Member States concerned a risk management plan and a summary thereof, where the marketing authorisation for the reference medicinal product is withdrawn but the marketing authorisation for the medicinal product referred to in Articles 9 and 11 is maintained.

   The risk management plan and the summary thereof shall be submitted to the competent authorities of the Member States concerned within 60 days of the withdrawal of the marketing authorisation for the reference medicinal product by means of a variation.

2. The competent authority of the Member State may impose an obligation on a marketing authorisation holder for a medicinal product referred to Articles 9 and 11 to submit a risk management plan and summary thereof where:

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

   (b) it is justified on pharmacovigilance grounds.

3. In the case referred to in paragraph 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.

Article 92

Variation of marketing authorisation

1. An application for variation of a marketing authorisation by the marketing authorisation holder shall be made electronically in the formats made available by the Agency, unless

the variation is an update by the marketing authorisation holder of their information held in a database.

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

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

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

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

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

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

   (d) specifying exemptions to the variation procedures where the update of information in the marketing authorisation referred to in Annex 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 93

Variation of marketing authorisation under the decentralised or mutual recognition procedure

1. Any application by the marketing authorisation holder to vary a marketing authorisation that has been granted in accordance with the provisions of Chapter III, Sections 3 and 4, shall be submitted to all the Member States that have previously authorised the medicinal product concerned. The same shall apply where the initial marketing authorisations were granted through separate procedures.

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

Article 94

Variation of marketing authorisations on the basis of paediatric studies

1. On the basis of relevant paediatric clinical studies received in accordance with Article 45(1) of Regulation (EC) No 1901/2006 of the European Parliament and of the Council[39], the competent authorities of the Member States may vary the marketing authorisation of the medicinal product concerned accordingly and update the summary of product characteristics and package leaflet of the medicinal product concerned. The competent authorities shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisations concerned.

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

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

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

5. The Agency shall coordinate the exchange of information.

Article 95

Union interest referral procedure

1. The Member States or the Commission shall, in specific cases where the interests of the Union are involved, refer the matter to the Committee for Medicinal Products for Human Use for the application of the procedure laid down in Articles 41 and 42 before any decision is reached on an application for a marketing authorisation or on the suspension or revocation of a marketing authorisation, or on any other variation of the marketing authorisation that appears necessary. The Member States and the Commission shall take due account of any requests by the applicant or the marketing authorisation holder.

   Where the referral results from the evaluation of data relating to pharmacovigilance of an authorised medicinal product, the matter shall be referred to the Pharmacovigilance Risk Assessment Committee and Article 115(2) may be applied. The Pharmacovigilance Risk Assessment Committee shall issue a recommendation according to the procedure laid down in Article 41. The final recommendation shall be forwarded to the Committee for Medicinal Products for Human Use or to the coordination group, as appropriate, and the procedure laid down in Article 115 shall apply.

[39] 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).

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

The Member State concerned or the Commission shall clearly identify the question that is referred to the Committee for consideration and shall inform the applicant or the marketing authorisation holder.

The Member States and the applicant or the marketing authorisation holder shall supply the Committee with all available information relating to the matter in question.

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

In that event, Article 93 shall apply to those medicinal products only if they were covered by the authorisation procedures referred to in Chapter III, Sections 3 and 4.

Where the scope of the procedure initiated under this Article concerns a range of medicinal products or a therapeutic class, medicinal products covered by a centralised marketing authorisation that belong to that range or class shall also be included in the procedure.

3. Without prejudice to paragraph 1, a Member State may, where urgent action is necessary to protect public health at any stage of the procedure, suspend the marketing authorisation and prohibit the use of the medicinal product concerned on its territory until a definitive decision is adopted. It shall inform the Commission, the Agency and the other Member States, no later than the following working day, of the reasons for its action.

4. Where the scope of the procedure initiated under this Article, as determined in accordance with paragraph 2, includes medicinal products covered by a centralised marketing authorisation, the Commission may, where urgent action is necessary to protect public health, at any stage of the procedure suspend the marketing authorisations and prohibit the use of the medicinal products concerned until a definitive decision is adopted. The Commission shall inform the Agency and the Member States no later than the following working day of the reasons for its action.

Chapter IX
Pharmacovigilance

SECTION 1

GENERAL PROVISIONS

Article 96

Member State pharmacovigilance system

1. Member States shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and their participation in the Union pharmacovigilance activities.

The pharmacovigilance system shall be used to collect information on the risks of medicinal products as regards health of the patients or the public. That information shall in particular refer to adverse reactions in human beings, arising from use of the medicinal product within the terms of the marketing authorisation as well as from use outside the terms of the marketing authorisation, and to adverse reactions associated with occupational exposure.

2. Member States shall, by means of the pharmacovigilance system referred to in paragraph 1, evaluate all information scientifically, consider options for risk minimisation and prevention and take regulatory action concerning the marketing authorisation as necessary. They shall perform a regular audit of their pharmacovigilance system and take corrective actions if necessary.

3. Each Member State shall designate a competent authority for the performance of pharmacovigilance tasks.

4. The Commission may request the Member States to participate, under the coordination of the Agency, in international harmonisation and standardisation of technical measures in relation to pharmacovigilance.

Article 97

Member State responsibilities for pharmacovigilance activities

1. The Member States shall:

(a) take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected adverse reactions to the competent authority of the Member State and may involve organisations representing consumers, patients and healthcare professionals for those tasks where appropriate;

(b) facilitate patient reporting through the provision of alternative reporting formats in addition to web-based formats;

(c) take all appropriate measures to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports;

(d) ensure that the public is given important information on pharmacovigilance concerns relating to the use of a medicinal product in a timely manner through publication on the web-portal and through other means of publicly available information as necessary;

(e) ensure, through the methods for collecting information and where necessary through the follow-up of suspected adverse reaction reports, that all appropriate measures are taken to identify clearly any biological medicinal product prescribed, dispensed, or sold in their territory that is the subject of a suspected adverse reaction report, with due regard to the name of the medicinal product, and the batch number.

2. For the purposes of paragraph 1, points (a) and (e), the Member States may impose specific obligations on doctors, pharmacists and other healthcare professionals.

Article 98

Member State delegation of pharmacovigilance tasks

1. A Member State may delegate any of the tasks entrusted to it under this Chapter to another Member State subject to a written agreement of the latter. Each Member State may represent no more than one other Member State.

2. The delegating Member State shall inform the Commission, the Agency and all other Member States of the delegation in writing. The delegating Member State and the Agency shall make that information publicly available.

Article 99

Marketing authorisation holder pharmacovigilance system

1. Marketing authorisation holders shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks equivalent to the relevant Member State's pharmacovigilance system referred to in Article 96(1).

2. Marketing authorisation holders shall by means of the pharmacovigilance system referred to in Article 96(1) evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary.

3. Marketing authorisation holders shall perform a regular audit of their pharmacovigilance system. They shall place a note concerning the main findings of the audit on the pharmacovigilance system master file and, based on the audit findings, ensure that an appropriate corrective action plan is prepared and implemented. Once the corrective actions have been fully implemented, the note may be removed.

4. As part of the pharmacovigilance system, marketing authorisation holders shall:

   (a) have permanently and continuously at their disposal an appropriately qualified person responsible for pharmacovigilance;

   (b) maintain and make available on request by a competent authority a pharmacovigilance system master file;

   (c) operate a risk management system for each medicinal product;

   (d) monitor the outcome of risk minimisation measures that are contained in the risk management plan pursuant to Article 21 or that are laid down as conditions of the marketing authorisation pursuant to Articles 44, 45 and any obligations imposed in accordance with Article 87;

   (e) update the risk management system and monitor pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products.

5. The qualified person referred to in paragraph 4, point (a), shall reside and operate in the Union and shall be responsible for the establishment and maintenance of the pharmacovigilance system. The marketing authorisation holder shall submit the name and

contact details of the qualified person to the competent authority of the Member State and the Agency.

6. The marketing authorisation holder shall, on request from the competent authority of a Member State, nominate a contact person for pharmacovigilance issues in that Member State who shall report to the qualified person referred to in paragraph 4, point (a).

Article 100

Risk management system

1. Holders of marketing authorisations granted before 21 July 2012 shall, by way of derogation from Article 99(4), point (c), not be required to operate a risk management system for each medicinal product.

2. The competent authority of a Member State may impose an obligation on a marketing authorisation holder of a national marketing authorisation to operate a risk management system, as referred to in Article 99(4), point (c), if there are concerns about the risks affecting the benefit-risk balance of an authorised medicinal product. In that context, the competent authority of a Member State shall also oblige the marketing authorisation holder to submit a risk management plan for the risk management system that they intend to introduce for the medicinal product concerned.

3. The obligation referred to in paragraph 2 shall be duly justified, notified in writing, and shall include the timeframe for submission of the risk management plan.

4. The competent authority of a Member State shall provide the 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.

5. On the basis of the written observations submitted by the marketing authorisation holder, the competent authority of a Member State shall withdraw or confirm the obligation. Where the competent authority of a Member State confirms the obligation, the marketing authorisation shall be varied accordingly to include the measures to be taken as part of the risk management system as conditions of the marketing authorisation referred to in Article 44, point (a).

Article 101

Funds for pharmacovigilance activities

1. The management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance shall be under the permanent control of the competent authorities of the Member States in order to guarantee their independence in the performance of those pharmacovigilance activities.

2. Paragraph 1 shall not preclude the competent authorities of the Member States from charging fees to marketing authorisation holders for performing pharmacovigilance

activities on the condition that the independence in the performance of those pharmacovigilance activities is strictly guaranteed.

SECTION 2

TRANSPARENCY AND COMMUNICATIONS

Article 102

National web-portal

1. Each Member State shall set up and maintain a national medicines web-portal which shall be linked to the European medicines web-portal established in accordance with Article 104 of [revised Regulation (EC) No 726/2004]. By means of the national medicines web-portals, the Member States shall make publicly available at least the following:

   (a) public assessment reports, together with a summary thereof;

   (b) summaries of product characteristics and package leaflets;

   (c) summaries of risk management plans for medicinal products covered by a national marketing authorisation in accordance with Chapter III;

   (d) information on the different ways of reporting suspected adverse reactions to medicinal products to competent authorities of the Member States by healthcare professionals and patients, including the web-based structured forms referred to in Article 102 of [revised Regulation (EC) No 726/2004].

2. The summaries referred to in paragraph 2, point (c), shall include, where relevant, a description of additional risk minimisation measures.

Article 103

Publication of assessment

The Agency shall make publicly available the final assessment conclusions, recommendations, opinions and decisions referred to in Articles 107 to 116, by means of the European medicines web-portal.

Article 104

Public announcements

1. As soon as the marketing authorisation holder intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product, and in any event at the same time or before the public announcement is made, they shall be required to inform the competent authorities of the Member States, the Agency and the Commission.

2. The marketing authorisation holder shall ensure that information to the public is presented objectively and is not misleading.

3. Unless urgent public announcements are required for the protection of public health, the Member States, the Agency and the Commission shall inform each other not less than 24 hours prior to a public announcement relating to information on pharmacovigilance concerns.

4. For active substances contained in medicinal products authorised in more than one Member State, the Agency shall be responsible for the coordination between competent authorities of the Member States of safety announcements and shall provide timetables for the information being made publicly available.

5. Under the coordination of the Agency, the Member States shall make all reasonable efforts to agree on a common message in relation to the safety of the medicinal product concerned and the timetables for their distribution. The Pharmacovigilance Risk Assessment Committee shall, at the request of the Agency, provide advice on those safety announcements.

6. When the Agency or competent authorities of the Member States make publicly available information referred to in paragraphs 2 and 3, any personal data or data of a commercially confidential nature shall be deleted unless its public disclosure is necessary for the protection of public health.

SECTION 3

RECORDING AND REPORTING OF SUSPECTED ADVERSE REACTIONS

Article 105

Recording and reporting of suspected adverse reactions by the marketing authorisation holder

1. Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries that are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study including data relating to off-label use of the product.

   Marketing authorisation holders shall ensure that those reports are accessible at a single point within the Union.

   By way of derogation from the first subparagraph, suspected adverse reactions occurring in the context of a clinical trial shall be recorded and reported in accordance with Regulation (EU) No 536/2014.

2. Marketing authorisation holders shall not refuse to consider reports of suspected adverse reactions received electronically or by any other appropriate means from patients or healthcare professionals.

3. Marketing authorisation holders shall submit electronically to the database and data-processing network referred to in Article 101 of [revised Regulation (EC) No 726/2004] ('Eudravigilance database') information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

Marketing authorisation holders shall submit electronically to the Eudravigilance database information on all non-serious suspected adverse reactions that occur in the Union, within 90 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

For medicinal products containing active substances referred to in the list of publications monitored by the Agency pursuant to Article 105 of [revised Regulation (EC) No 726/2004], marketing authorisation holders shall not be required to report to the Eudravigilance database the suspected adverse reactions recorded in the listed publications, but they shall monitor all other medical literature and report any suspected adverse reactions recorded therein.

4. Marketing authorisation holders shall establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports. They shall also collect follow-up information on those reports and submit the updates to the Eudravigilance database.

5. Marketing authorisation holders shall collaborate with the Agency and the competent authorities of the Member States in the detection of duplicates of suspected adverse reaction reports.

6. This Article shall apply *mutatis mutandis* to undertakings supplying medicinal products used in accordance with Article 3, paragraphs 1 or 2.

Article 106

Recording and reporting of suspected adverse reactions by Member States

1. Each Member State shall record all suspected adverse reactions that occur in its territory and that are brought to its attention from healthcare professionals and patients. This shall include all authorised medicinal products and medicinal products used in accordance with Article 3, paragraphs 1 or 2. Member States shall involve patients and healthcare professionals, as appropriate, in the follow-up of any reports they receive in order to comply with Article 97(1), points (c) and (e).

Member States shall ensure that reports of such reactions may be submitted by means of the national medicines web-portals or by other means.

2. For reports submitted by a marketing authorisation holder, Member States on whose territory the suspected adverse reaction occurred may involve the marketing authorisation holder in the follow-up of the reports.

3. Member States shall collaborate with the Agency and the marketing authorisation holders in the detection of duplicates of suspected adverse reaction reports.

4. Member States shall, within 15 days following the receipt of the reports of serious suspected adverse reactions referred to in paragraph 1, submit the reports electronically to the Eudravigilance database.

Member States shall, within 90 days from the receipt of the reports referred to in paragraph 1, submit reports of non-serious suspected adverse reactions electronically to the Eudravigilance database.

Marketing authorisation holders shall have access to the reports referred to in this paragraph through the Eudravigilance database.

5. Member States shall ensure that reports of suspected adverse reactions arising from an error associated with the use of a medicinal product that are brought to their attention are made available to the Eudravigilance database and to any authorities, bodies, organisations or institutions, responsible for patient safety within that Member State concerned. They shall also ensure that the authorities responsible for medicinal products within that Member State are informed of any suspected adverse reactions brought to the attention of any other authority within that Member State. These reports shall be appropriately identified in the forms referred to in Article 102 of [revised Regulation (EC) No 726/2004].

6. Unless there are justifiable grounds resulting from pharmacovigilance activities, Member States shall not impose any additional obligations on marketing authorisation holders for the reporting of suspected adverse reactions.

SECTION 4

PERIODIC SAFETY UPDATE REPORTS

Article 107

Periodic safety update reports

1. Marketing authorisation holders shall submit to the Agency periodic safety update reports containing:

   (a) summaries of data relevant to the benefit-risk balance of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorisation;

   (b) a scientific evaluation of the benefit-risk balance of the medicinal product;

   (c) all data relating to the volume of sales of the medicinal product and any data in possession of the marketing authorisation holder relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product.

   The data provided in accordance with the first subparagraph, point (c), shall differentiate between sales and volumes generated within the Union and those generated outside the Union.

2. The evaluation referred to in paragraph 1, first subparagraph, point (b), shall be based on all available data, including data from clinical trials in unauthorised therapeutic indications and populations.

The periodic safety update reports shall be submitted electronically.

3. The Agency shall make available the reports referred to in paragraph 1 to the competent authorities of the Member States, the members of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group by means of the repository referred to in Article 103 of [revised Regulation (EC) No 726/2004].

4. By way of derogation from paragraph 1, the marketing authorisation holders for medicinal products referred to in Articles 9, or 13, and the registration holders for medicinal products referred to in Articles 126 or 134(1), shall only be required to submit periodic safety update reports for such medicinal products to the competent authority in the following cases:

(a) where such obligation has been laid down as a condition in the marketing authorisation in accordance with Articles 44 or 45; or

(b) when requested by a competent authority on the basis of concerns relating to pharmacovigilance data or due to the lack of periodic safety update reports relating to an active substance after the marketing authorisation has been granted.

The assessment reports of the periodic safety update reports referred to in the first subparagraph shall be communicated by the competent authority to the Pharmacovigilance Risk Assessment Committee, which shall consider whether there is a need for a single assessment report for all marketing authorisations for medicinal products containing the same active substance and which shall inform the coordination group or the Committee for Medicinal Products for Human Use accordingly, in order to apply the procedures laid down in Articles 108(4) and 110.

Article 108

Frequency of periodic safety update reports

1. The frequency with which the periodic safety update reports are to be submitted shall be specified in the marketing authorisation.

The dates of submission according to the specified frequency shall be calculated from the date when then marketing authorisation was granted.

2. Holders of marketing authorisations which have been granted before 21 July 2012, and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation, shall submit the periodic safety update reports in accordance with the second subparagraph until another frequency or other dates of submission of the reports are laid down in the marketing authorisation or determined in accordance with the paragraphs 4, 5 and 6.

Periodic safety update reports shall be submitted to the competent authorities immediately upon request:

(a) where a medicinal product has not yet been placed on the market, at least every six months following the marketing authorisation and until the placing on the market;

(b) where a medicinal product has been placed on the market, at least every six months during the first two years following the initial placing on the market, once a year for the following two years and at three-yearly intervals thereafter.

3. Paragraph 2 shall also apply to medicinal products that are authorised only in one Member State and for which paragraph 4 does not apply.

4. Where medicinal products that are subject to different marketing authorisations contain the same active substance or the same combination of active substances, the frequency and dates of submission of the periodic safety update reports resulting from the application of the paragraphs 1 and 2 may be amended and harmonised to enable a single assessment to be made in the context of a periodic safety update report work-sharing procedure and to set a Union reference date from which the submission dates to be calculated.

The harmonised frequency for the submission of the reports and the Union reference date may be determined, after consultation of the Pharmacovigilance Risk Assessment Committee, by one of the following:

(a) the Committee for Medicinal Products for Human Use, where at least one of the marketing authorisations for the medicinal products containing the active substance concerned has been granted in accordance with the centralised procedure provided for in Article 3 of [revised Regulation (EC) No 726/2004];

(b) the coordination group, in other cases than those referred to in point (a).

The harmonised frequency for the submission of the reports determined pursuant to the first and second subparagraphs shall be made publicly available by the Agency. Marketing authorisation holders shall submit an application for a variation of the marketing authorisation accordingly.

5. For the purposes of paragraph 4, the Union reference date for medicinal products containing the same active substance or the same combination of active substances shall be one of the following:

(a) the date when the first marketing authorisation was granted in the Union for a medicinal product containing that active substance or that combination of active substances;

(b) if the date referred to in point (a) cannot be ascertained, the earliest of the known dates of the marketing authorisations for a medicinal product containing that active substance or that combination of active substances.

6. Marketing authorisation holders shall be allowed to submit requests to the Committee for Medicinal Products for Human Use or the coordination group, as appropriate, to determine Union reference dates or to change the frequency of submission of periodic safety update reports on one of the following grounds:

(a) for reasons relating to public health;

(b) in order to avoid a duplication of the assessment;

(c) in order to achieve international harmonisation.

Such requests shall be submitted in writing and shall be duly justified. The Committee for Medicinal Products for Human Use or the coordination group shall, following the consultation with the Pharmacovigilance Risk Assessment Committee, either approve or deny such requests. Any change in the dates or the frequency of submission of periodic safety update reports shall be made publicly available by the Agency. The marketing authorisation holders shall submit an application for a variation of the marketing authorisation accordingly.

7. The Agency shall make public a list of Union reference dates and frequency of submission of periodic safety update reports by means of the European medicines web-portal.

Any change to the dates of submission and frequency of periodic safety update reports specified in the marketing authorisation as a result of the application of the paragraphs 4, 5 and 6 shall take effect four months after the date of the publication referred to in the first subparagraph.

Article 109

Assessment of periodic safety update reports

The competent authorities of the Member State shall assess periodic safety update reports to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products.

Article 110

Single assessment of periodic safety update reports

1. A single assessment of periodic safety update reports shall be performed for medicinal products authorised in more than one Member State and, in the cases referred to in Article 108, paragraphs 4, 5 and 6, for all medicinal products containing the same active substance or the same combination of active substances and for which a Union reference date and a frequency of periodic safety update reports has been established.

The single assessment shall be conducted by either of the following:

(a) a Member State appointed by the coordination group where none of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Article 3 of [revised Regulation (EC) No 726/2004];

(b) a rapporteur appointed by the Pharmacovigilance Risk Assessment Committee, where at least one of the marketing authorisations concerned has been granted in accordance with the centralised procedure provided for in Article 3 of [revised Regulation (EC) No 726/2004].

When selecting the Member State in accordance with the second subparagraph, point (a), the coordination group shall take into account whether any Member State is acting as a reference Member State, in accordance with Chapter III, Sections 3 and 4.

2. The Member State or rapporteur, as appropriate, 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 Member States concerned. The Agency shall send the report to the marketing authorisation holder.

   Within 30 days of receipt of the assessment report, the Member States and the marketing authorisation holder may submit comments to the Agency and to the rapporteur or Member State.

3. Following the receipt of the comments referred to in paragraph 2, the rapporteur or Member State 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 any 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 of [revised Regulation (EC) No 726/2004] and forward them to the marketing authorisation holder.

Article 111

Regulatory action on periodic safety update reports

Following the assessment of periodic safety update reports referred to in Article 107, the competent authorities of the Member States shall consider whether any action concerning the marketing authorisation for the medicinal product concerned is necessary and shall maintain, vary, suspend or revoke the marketing authorisation as appropriate.

Article 112

Procedure for regulatory action on periodic safety update reports

1. In the case of a single assessment of periodic safety update reports in accordance with Article 110(1) which recommends action concerning more than one marketing authorisation that does not include any centralised marketing authorisation, the coordination group shall, within 30 days of receipt of the assessment report of the Pharmacovigilance Risk Assessment Committee, consider the assessment report and reach a position on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the agreed position.

2. If, within the coordination group, the Member States represented reach an agreement on the action to be taken by consensus, the chairperson shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary, suspend or revoke the marketing

authorisations concerned in accordance with the timetable for implementation determined in the agreement.

In the event of a variation, the marketing authorisation holder shall submit to the competent authorities of the Member States an appropriate application for a modification, including an updated summary of product characteristics and an updated package leaflet within the determined timetable for implementation.

If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in Article 42.

Where the agreement reached by the Member States represented within the coordination group or the position of the majority of Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or the majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

3. In the case of a single assessment of periodic safety update reports in accordance with Article 110(1) that recommends action concerning more than one marketing authorisation that includes at least one centralised marketing authorisation, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisations concerned, including a timetable for the implementation of the opinion.

4. Where the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3 differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use shall attach to its opinion a detailed explanation of the scientific grounds for the differences together with the recommendation.

5. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall, by means of implementing acts:

   (a) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations granted by the Member States and concerned by the procedure provided for in this section; and

   (b) where the opinion states that regulatory action concerning the marketing authorisation is necessary, adopt a decision to vary, suspend or revoke the centralised marketing authorisations-and concerned by the procedure provided for in this section.

6. Article 42 shall apply to the adoption of the decision referred to in paragraph 5, point (a), and to its implementation by the Member States.

7. Article 13 of [revised Regulation (EC) No 726/2004] shall apply to the decision referred to in paragraph 5, point (b). Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 55 of [revised Regulation (EC) No 726/2004].

SECTION 5

SIGNAL DETECTION

Article 113

Signal monitoring and detection

1. Regarding medicinal products authorised in accordance with Chapter III, competent authorities of the Member States shall in collaboration with the Agency, take the following measures:

   (a) monitor the outcome of risk minimisation measures contained in risk management plans and of the conditions referred to in Articles 44, 45 and any obligations imposed in accordance with Article 87;

   (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.

3. The Agency and competent authorities of the Member States and the marketing authorisation holder shall inform each other in the event of new risks or risks that have changed or changes to the benefit-risk balance being detected.

4. Member States shall ensure that marketing authorisation holders inform the Agency and competent authorities of the Member State in the event of new risks or risks that have changed or when changes to the benefit-risk balance have been detected.

SECTION 6

URGENT UNION PROCEDURE

Article 114

Initiation of an urgent Union procedure

1. A Member State or the Commission, as appropriate, shall, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, initiate the

procedure provided for in this Section (the 'urgent Union procedure') by informing the other Member States, the Agency and the Commission where:

(a) it considers suspending or revoking a marketing authorisation;

(b) it considers prohibiting the supply of a medicinal product;

(c) it considers refusing the renewal of a marketing authorisation; or

(d) it is informed by the marketing authorisation holder that, on the basis of safety concerns, the marketing authorisation holder has interrupted the placing on the market of a medicinal product or has taken action to have a marketing authorisation withdrawn, or intends to take such action or has not applied for the renewal of a marketing authorisation.

2. A Member State or the Commission, as appropriate, shall, on the basis of concerns resulting from the evaluation of data from pharmacovigilance activities, inform the other Member States, the Agency and the Commission where it considers that a new contraindication, a reduction in the recommended dose or a restriction to the therapeutic indications of a medicinal product is necessary. The information shall outline the action considered and the reasons therefore.

Any Member State or the Commission, as appropriate, shall, when urgent action is considered necessary in any of the cases referred to in the first subparagraph, initiate the urgent Union procedure.

Where the urgent Union procedure is not initiated, for medicinal products authorised in accordance with Chapter III, Sections 3 and 4, the case shall be brought to the attention of the coordination group.

Article 95 shall apply where the interests of the Union are involved.

3. Where the urgent Union procedure is initiated, the Agency shall verify whether the safety concern relates to medicinal products other than the one covered by the information, or whether the safety concern is common to all medicinal products belonging to the same range or therapeutic class.

Where the medicinal product involved is authorised in more than one Member State, the Agency shall without undue delay inform the initiator of the urgent Union procedure of the outcome of the verification, and the procedures laid down in Articles 115 and 116 shall apply. Otherwise, the safety concern shall be addressed by the Member State concerned. The Agency or the Member State, as applicable, shall make the information that the urgent Union procedure has been initiated available to marketing authorisation holders.

4. Without prejudice to paragraphs 1 and 2, and Articles 115 and 116, a Member State may, where urgent action is necessary to protect public health, suspend the marketing authorisation and prohibit the use of the medicinal product concerned on its territory until a definitive decision is adopted in the urgent Union procedure. It shall inform the Commission, the Agency and the other Member States no later than the following working day of the reasons for its action.

5. At any stage of the procedure laid down in Articles 115 and 116, the Commission may request a Member State in which the medicinal product is authorised to take temporary measures immediately.

Where the scope of the procedure, as determined in accordance with paragraphs 1 and 2, includes medicinal products covered by centralised marketing authorisations, the Commission may, at any stage of the urgent Union procedure, take temporary measures immediately in relation to those marketing authorisations.

6. The information referred to in this Article may relate to individual medicinal products or to a range of medicinal products or a therapeutic class.

If the Agency identifies that the safety concern relates to more medicinal products than those that are covered by the information or that the safety concern is common to all medicinal products belonging to the same range or therapeutic class, it shall extend the scope of the procedure accordingly.

Where the scope of the urgent Union procedure concerns a range of medicinal products or therapeutic class, medicinal products covered by the centralised marketing authorisation, that belong to that range or class shall also be included in the procedure.

7. At the time the information referred to in paragraphs 1 and 2 is provided, the Member State shall make available to the Agency all relevant scientific information that it has at its disposal and any assessment by the Member State.

Article 115

Urgent Union procedure scientific assessment

1. Following receipt of the information referred to in Article 114, paragraphs 1 and 2, the Agency shall publicly announce the initiation of the urgent Union procedure by means of the European medicines web-portal. In parallel, Member States may publicly announce the initiation of the procedure on their national medicines web-portals.

The announcement shall specify the matter submitted to the Agency in accordance with Article 114, and the medicinal products and, where applicable, the active substances concerned. It shall contain information on the right of the marketing authorisation holders, healthcare professionals and the public to submit to the Agency information relevant to the procedure and it shall state how such information may be submitted.

2. The Pharmacovigilance Risk Assessment Committee shall assess the matter that has been submitted to the Agency in accordance with Article 114. The rapporteur, as referred to in Article 152 of [revised Regulation (EC) No 726/2004], shall closely collaborate with the rapporteur appointed by the Committee for Medicinal Products for Human Use and with the reference Member State for the medicinal products concerned.

For the purposes of the assessment referred to in the first subparagraph, the marketing authorisation holder may submit comments in writing.

Where the urgency of the matter permits, the Pharmacovigilance Risk Assessment Committee may hold public hearings, where it considers that this is appropriate on justified

grounds particularly with regard to the extent and seriousness of the safety concern. The hearings shall be held in accordance with the modalities specified by the Agency and shall be announced by means of the European medicines web-portal. The announcement shall specify the modalities of participation.

The Agency shall, in consultation with the parties concerned, draw up Rules of Procedure on the organisation and conduct of public hearings, in accordance with Article 163 of [revised Regulation (EC) No 726/2004].

Where a marketing authorisation holder or another person intending to submit information, has confidential data relevant to the subject matter of the procedure, they may request permission to present that data to the Pharmacovigilance Risk Assessment Committee in a non-public hearing.

3. Within 60 days of the submission of the information, the Pharmacovigilance Risk Assessment Committee shall make a recommendation, stating the reasons on which it is based, having due regard to the therapeutic effect of the medicinal product. The recommendation shall mention any divergent positions and the grounds on which they are based. In the case of urgency, and on the basis of a proposal by its chairperson, the Pharmacovigilance Risk Assessment Committee may agree to a shorter deadline. The recommendation shall include any or a combination of the following conclusions:

   (a) no further evaluation or action is required at Union level;

   (b) the marketing authorisation holder should conduct further evaluation of data and carry out a follow-up of the results of that evaluation;

   (c) the marketing authorisation holder should sponsor a post-authorisation safety study and carry out a follow up evaluation of the results of that study;

   (d) the Member States or marketing authorisation holder should implement risk minimisation measures;

   (e) the marketing authorisation should be suspended, revoked or not renewed;

   (f) the marketing authorisation should be varied.

4. For the purposes of paragraph 3, point (d), the recommendation shall specify the risk minimisation measures recommended and any conditions or restrictions to which the marketing authorisation should be made subject, including the timeline for implementation.

5. For the purposes of paragraph 3, point (f), where it is recommended to change or add information in the summary of product characteristics or the labelling or package leaflet, the recommendation shall suggest the wording of such changed or added information and shall indicate where in the summary of product characteristics, the labelling or package leaflet such wording should be placed.

Article 116

Follow-up of recommendation made in the framework of the urgent Union procedure

1. Where the scope of the urgent Union procedure, as determined in accordance with Article 114(6), does not include any centralised marketing authorisation, the coordination group shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee, consider the recommendation and reach a position on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisation concerned, including a timetable for the implementation of the agreed position. Where an urgent adoption of the position is necessary, the coordination group may, on the basis of a proposal by its chairperson, agree to a shorter deadline.

2. If, within the coordination group, the Member States represented reach an agreement on the action to be taken by consensus, the chairperson shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to maintain, vary, suspend, revoke or refuse renewal of the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

   In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the competent authorities of the Member States an appropriate application for a variation, including an updated summary of product characteristics and an updated package leaflet within the determined timetable for implementation.

   If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission which shall apply the procedure laid down in Article 42.

   Where the agreement reached by the Member States represented within the coordination group or the position of the majority of the Member States represented within the coordination group differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

3. Where the scope of the procedure, as determined in accordance with Article 114(6), includes at least one centralised marketing authorisation, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the recommendation of the Pharmacovigilance Risk Assessment Committee, consider the recommendation and adopt an opinion on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisations concerned. Where an urgent adoption of the opinion is necessary, the Committee for Medicinal Products for Human Use may, on the basis of a proposal by its chairperson, agree to a shorter deadline.

   Where the opinion of the Committee for Medicinal Products for Human Use 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.

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall, by means of implementing acts:

   (a) adopt a decision addressed to the Member States concerning the measures to be taken in respect of marketing authorisations that are granted by the Member States and that are subject to the urgent Union procedure;

(b) where the opinion states that regulatory action concerning the marketing authorisation is necessary, adopt a decision to vary, suspend, revoke or refuse the renewal of the centralised marketing authorisations and concerned by the procedure provided for in this section.

5. Article 42 shall apply to the adoption of the decision referred to in paragraph 4, point (a), and to its implementation by the Member States.

6. Article 13 of [revised Regulation (EC) No 726/2004] shall apply to the decision referred to in paragraph 4, point (b). Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 55 of [revised Regulation (EC) No 726/2004].

SECTION 7

SUPERVISION OF POST-AUTHORISATION SAFETY STUDIES

Article 117

Non-interventional post-authorisation safety studies

1. This Section applies to non-interventional post-authorisation safety studies that are initiated, managed or financed by the marketing authorisation holder voluntarily or pursuant to obligations imposed in accordance with Articles 44 or 87, and that involve the collection of safety data from patients or healthcare professionals.

2. This Section is without prejudice to Member States and Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorisation safety studies.

3. The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.

4. Payments to healthcare professionals for participating in non-interventional post-authorisation safety studies shall be restricted to the compensation for time and expenses incurred.

5. The competent authority of the Member State may require the marketing authorisation holder to submit the protocol and the progress reports to the competent authorities of the Member States in which the study is conducted.

6. The marketing authorisation holder shall send the final report of the study to the competent authorities of the Member States in which the study was conducted within 12 months of the end of data collection.

7. While a study is being conducted, the marketing authorisation holder shall monitor the data generated and consider its implications for the benefit-risk balance of the medicinal product concerned.

Any new information that might influence the evaluation of the benefit-risk balance of the medicinal product shall be communicated to the competent authorities of the Member State in which the medicinal product has been authorised in accordance with Article 90.

The obligation laid down in the second subparagraph is without prejudice to the information on the results of studies that the marketing authorisation holder shall make available by means of the periodic safety update reports as laid down in Article 107.

8. Articles 118 to 121 shall apply exclusively to studies referred to in paragraph 1 that are conducted pursuant to an obligation imposed in accordance with Articles 44 or 87.

Article 118

Agreement of a protocol for a non-interventional post-authorisation safety study

1. Before a study is conducted, the marketing authorisation holder shall submit a draft protocol to the Pharmacovigilance Risk Assessment Committee, except for studies to be conducted in only one Member State that requests the study in accordance with Article 87. For such studies, the marketing authorisation holder shall submit a draft protocol to the competent authority of the Member State in which the study is conducted.

2. Within 60 days of the submission of the draft protocol referred to in paragraph 1 the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall issue:

   (a) a letter endorsing the draft protocol;

   (b) a letter of objection, which shall set out in detail the grounds for the objection, where:

      (i) it considers that the conduct of the study promotes the use of a medicinal product;

      (ii) it considers that the design of the study does not fulfil the study objectives; or

   (c) a letter notifying the marketing authorisation holder that the study is a clinical trial falling under the scope of Regulation (EU) No 536/2014.

3. The study may commence only when the written endorsement from the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee, as appropriate, has been issued.

   Where a letter of endorsement of the draft protocol as referred to in paragraph 2, point (a), has been issued, the marketing authorisation holder shall forward the protocol to the competent authorities of the Member States in which the study is to be conducted and may thereafter commence the study according to the endorsed protocol.

Article 119

Update of a protocol for a non-interventional post-authorisation safety study

After a study has been commenced, any substantial amendments to the protocol shall be submitted, before their implementation, to the competent authority of the Member State or to the Pharmacovigilance Risk Assessment Committee, as appropriate. The competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee, as appropriate, shall assess the amendments and inform the marketing authorisation holder of its endorsement or objection. Where applicable, the marketing authorisation holder shall inform the Member States in which the study is conducted.

Article 120

Final study report on a non-interventional post-authorisation safety study

1. Upon completion of the study, a final study report shall be submitted to the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee within 12 months of the end of data collection unless a written waiver has been granted by the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee, as appropriate.

2. The marketing authorisation holder shall evaluate whether the results of the study have an impact on the marketing authorisation and shall, if necessary, submit to the competent authorities of the Member States an application to vary the marketing authorisation.

3. Together with the final study report, the marketing authorisation holder shall electronically submit an abstract of the study results to the competent authority of the Member State or the Pharmacovigilance Risk Assessment Committee.

Article 121

Recommendations following the submission of a final study report on non-interventional post-authorisation safety studies

1. Based on the results of the study and after consultation of the marketing authorisation holder, the Pharmacovigilance Risk Assessment Committee may make recommendations concerning the marketing authorisation, stating the reasons on which they are based. The recommendations shall mention any divergent positions and the grounds on which they are based.

2. When recommendations for the variation, suspension or revocation of a national marketing authorisation are made, the Member States represented within the coordination group shall agree on a position on the matter taking into account the recommendation referred to in paragraph 1 and shall include a timetable for the implementation of the agreed position.

   If, within the coordination group, the Member States represented reach an agreement on the action to be taken by consensus, the chairperson shall record the agreement and send it to the marketing authorisation holder and the Member States. The Member States shall adopt necessary measures to vary, suspend or revoke the marketing authorisation concerned in accordance with the implementation timetable determined in the agreement.

   In the event that a variation is agreed upon, the marketing authorisation holder shall submit to the competent authorities of the Member State an appropriate application for a variation,

including an updated summary of product characteristics and an updated package leaflet within the determined timetable for implementation.

The agreement shall be made publicly available on the European medicines web-portal established in accordance with Article 104 of [revised Regulation (EC) No 726/2004].

3. If an agreement by consensus cannot be reached, the position of the majority of the Member States represented within the coordination group shall be forwarded to the Commission, which shall apply the procedure laid down in Article 42.

4. Where the agreement reached by the Member States represented within the coordination group or the position of the majority of Member States differs from the recommendation of the Pharmacovigilance Risk Assessment Committee, the coordination group shall attach to the agreement or majority position a detailed explanation of the scientific grounds for the differences together with the recommendation.

SECTION 8

IMPLEMENTATION, GUIDANCE AND REPORTING

Article 122

Implementing measures related to pharmacovigilance activities

1. In order to harmonise the performance of the pharmacovigilance activities provided for in this Directive, the Commission shall adopt implementing measures in the following areas for which pharmacovigilance activities are provided for in Annex I, Articles 96, 99, 100, 105 to 107, 113, 118 and 120 by setting out:

   (a) the content and the rules on the maintenance of the pharmacovigilance system master file kept by the marketing authorisation holder;

   (b) minimum requirements for the quality system for the performance of pharmacovigilance activities by the competent authorities of the Member States and the marketing authorisation holder;

   (c) rules on the use of internationally agreed terminology, formats and standards for the performance of pharmacovigilance activities;

   (d) minimum requirements for the monitoring of data in the Eudravigilance database to determine whether there are new risks or whether risks have changed;

   (e) the format and content of the electronic transmission of suspected adverse reactions by Member States and the marketing authorisation holder;

   (f) the format and content of electronic periodic safety update reports and risk management plans;

   (g) the format of protocols, abstracts and final study reports for the post-authorisation safety studies.

2. Those measures shall take account of the work on international harmonisation carried out in the area of pharmacovigilance. Those measures shall be adopted in accordance with the regulatory procedure referred to in Article 214(2).

Article 123

Guidance to facilitate the performance of pharmacovigilance activities

The Agency shall, in cooperation with competent authorities of the Member States and other interested parties, draw up:

(a) guidance on good pharmacovigilance practices for both competent authorities and marketing authorisation holders;

(b) scientific guidance on post-authorisation efficacy studies.

Article 124

Reporting on pharmacovigilance tasks

The Agency shall make public a report on the performance of pharmacovigilance tasks by the Member States and the Agency every three years. The first report shall be made public by [three years after application date of [revised Regulation (EC) No 726/2004].

Chapter X
Homeopathic medicinal products and traditional herbal medicinal products

SECTION 1

SPECIFIC PROVISIONS APPLICABLE TO HOMEOPATHIC MEDICINAL PRODUCTS

Article 125

Registration or authorisation of homeopathic medicinal products

1. Member States shall ensure that homeopathic medicinal products manufactured and placed on the market in the Union are registered in accordance with Articles 126 and 127 or authorised in accordance with Article 133(1), except where such homeopathic medicinal products are covered by a registration or authorisation granted in accordance with national legislation on or before 31 December 1993. In case of registrations, Chapter III, Sections 3 and 4, and Article 38, paragraphs 1, 2 and 3 shall apply.

2. Member States shall establish a simplified registration procedure referred to in Article 126 for the homeopathic medicinal products.

Article 126

Simplified registration procedure for homeopathic medicinal products

1. Homeopathic medicinal products that satisfy all of the following conditions may be subject to a simplified registration procedure:

   (a) they are administered orally or externally;

   (b) no specific therapeutic indication appears on the labelling of the medicinal product or in any information relating thereto;

   (c) there is a sufficient degree of dilution to guarantee the safety of the medicinal product.

   For the purposes of point (c), the medicinal product may not contain either more than one part per 10000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription.

   The Commission is empowered to adopt delegated acts in accordance with Article 215 to amend the first subparagph, point (c), in order to take account of scientific progress.

   At the time of registration, Member States shall determine the prescription status for the dispensing of the homeopathic medicinal product.

2. The criteria and rules of procedure provided for in Article 1(10), point (c), Article 30, Chapter III, Section 6, Articles 191, 195 and 204 shall apply by analogy to the simplified registration procedure for homeopathic medicinal products, with the exception of the proof of therapeutic efficacy.

Article 127

Application requirements for simplified registration

An application a simplified registration may cover a series of homeopathic medicinal products derived from the same homeopathic stock or stocks. The following shall be included with the application in order to demonstrate, in particular, the pharmaceutical quality and the batch-to-batch homogeneity of the homeopathic medicinal products concerned:

(a) the scientific name or other name given in a pharmacopoeia of the homeopathic stock or stocks, together with a statement of the various routes of administration, pharmaceutical forms and degree of dilution to be registered;

(b) a dossier describing how the homeopathic stock or stocks are obtained and controlled, and justifying their homeopathic use, on the basis of an adequate bibliography;

(c) the manufacturing and control file for each pharmaceutical form and a description of the method of dilution and potentisation;

(d) the manufacturing authorisation for the homeopathic medicinal product concerned;

(e) the copies of any registrations or authorisations obtained for the same homeopathic medicinal product in other Member States;

(f) one or more mock-ups of the outer packaging and the immediate packaging of the homeopathic medicinal products to be registered;

(g) the data concerning the stability of the homeopathic medicinal product.

Article 128

Application of decentralised and mutual recognition procedures to homeopathic medicinal products

1. Article 38, paragraphs 4 and 6, Articles 39 to 42 and 95 shall not apply to the homeopathic medicinal products referred to in Article 126.

2. Chapter III, Sections 3 to 5, shall not apply to the homeopathic medicinal products referred to in Article 133(2).

Article 129

Labelling of homeopathic medicinal products

Homeopathic medicinal products, with the exception those referred to in Article 126(1), shall be labelled in accordance with the provisions of Chapter VI and shall be identified by a reference on their labels, in clear and legible form, to their homeopathic nature.

Article 130

Specific requirements for labelling of certain homeopathic medicinal products

1. The labelling and, where appropriate, the package insert for homeopathic medicinal products referred to in Article 126(1) in addition to the clear mention of the words 'homeopathic medicinal product', shall bear the following, and no other, information:

   (a) the scientific name of the stock or stocks followed by the degree of dilution, making use of the symbols of the pharmacopoeia used in accordance with Article 4(62);

   (b) name and address of the registration holder and, where appropriate, of the manufacturer;

   (c) method of administration and, if necessary, route of administration;

   (d) pharmaceutical form;

   (e) expiry date, in clear terms (month, year);

   (f) contents of the sales presentation;

   (g) special storage precautions, if any;

   (h) a special warning if necessary for the medicinal product;

(i) manufacturer's batch number;

(j) registration number;

(k) ‘homeopathic medicinal product without approved therapeutic indications’;

(l) a warning advising the user to consult a doctor if the symptoms persist.

As regards the first subparagraph, point (a), if the homeopathic medicinal product is composed of two or more stocks, the scientific names of the stocks on the labelling may be supplemented by an invented name.

2. Notwithstanding paragraph 1, Member States may require the use of certain types of labelling in order to show:

(a) the price of the homeopathic medicinal product;

(b) the conditions for refunds by social security bodies.

Article 131

Advertising of homeopathic medicinal products

1. Chapter XIII shall apply to homeopathic medicinal products.

2. By derogation from paragraph 1, Article 176(1) shall not apply to medicinal products referred to in Article 126(1).

However, only the information specified in Article 130(1) may be used in the advertising of such homeopathic medicinal products.

Article 132

Exchange of information on homeopathic medicinal products

Member States shall communicate to each other all the information necessary to guarantee the quality and safety of homeopathic medicinal products manufactured and marketed within the Union, and in particular the information referred to in Articles 202 and 203.

Article 133

Other requirements for homeopathic medicinal products

1. Homeopathic medicinal products other than those referred to in Article 126(1) shall be granted a marketing authorisation in accordance with Articles 6 and 9 to 14 and labelled in accordance with Chapter VI.

2. A Member State may introduce or retain in its territory specific rules for the non-clinical tests and clinical studies of homeopathic medicinal products other than those referred to in Article 126(1), in accordance with the principles and characteristics of homeopathy as practised in that Member State.

In this case, the Member State concerned shall notify the Commission of the specific rules in force.

3. Chapter IX shall apply to homeopathic medicinal products, with the exception of those referred to in Article 126(1). Chapter XI, Chapter XII, Section 1, and Chapter XIV shall apply to homeopathic medicinal products.

SECTION 2

SPECIFIC PROVISIONS APPLICABLE TO TRADITIONAL HERBAL MEDICINAL PRODUCTS

Article 134

Simplified registration procedure for traditional herbal medicinal products

1. Herbal medicinal products that satisfy all of the following conditions may be subject to a simplified registration procedure ('traditional-use registration'):

   (a) they have therapeutic indications exclusively appropriate to traditional herbal medicinal products that, by virtue of their composition and purpose, are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment;

   (b) they are exclusively for administration in accordance with a specified strength and posology;

   (c) they are an oral, external or inhalation preparation;

   (d) the period of traditional use as laid down in Article 136(1), point (c), has elapsed;

   (e) the data on the traditional use of the herbal medicinal product referred to in Article 136(1), point (c), are sufficient.

   The data on the use of a medicinal product referred to in the first subparagraph, point (e), shall be considered sufficient where the herbal medicinal product proves not to be harmful in the specified conditions of use and the pharmacological effects or efficacy of the herbal medicinal product are plausible on the basis of long-standing use and experience.

2. Notwithstanding Article 4(1), point (64), the presence in the herbal medicinal product of vitamins or minerals for the safety of which there is well-documented evidence shall not prevent the herbal medicinal product from being eligible for registration in accordance with paragraph 1, provided that the action of the vitamins or minerals is ancillary to that of the herbal active substances regarding the specified claimed therapeutic indication(s).

3. However, in cases where the competent authorities judge that a herbal medicinal product that fulfils the conditions laid down in paragraph 1 ('traditional herbal medicinal product') fulfils the criteria for a national marketing authorisation in accordance with Article 5 or for a simplified registration in accordance with Article 126, the provisions of this Section shall not apply.

Article 135

Submission of dossier for traditional herbal medicinal product

1. The applicant and the traditional-use registration holder shall be established in the Union.

2. In order to obtain a traditional-use registration, the applicant shall submit an application to the competent authority of the Member State concerned.

Article 136

Application requirements for traditional-use registration

1. An application for traditional-use registration shall be accompanied by:

   (a) the particulars and documentation:

      (i) referred to in points (1), (2), (3), (5) to (9), (16) and (17) of Annex I;

      (ii) the results of the pharmaceutical tests referred to in Annex I;

      (iii) the summary of product characteristics, without the clinical particulars as specified in Annex V;

      (iv) in case of combinations, as referred to in Article 4(1), point (64), or in Article 134(2), the information referred to in Article 134(1), first subparagraph, point (e), relating to the combination as such; if the individual active substances are not sufficiently known, the data shall also relate to the individual active substances;

   (b) any national marketing authorisation or registration obtained by the applicant in another Member State, or in a third country, to place the herbal medicinal product on the market, and details of any decision to refuse to grant a national marketing authorisation or registration, whether in the Union or a third country, and the reasons for any such decision;

   (c) bibliographical or expert evidence to the effect that the herbal medicinal product in question, or a corresponding medicinal product has been in medicinal use throughout a period of at least 30 years preceding the date of the application, including at least 15 years within the Union;

   (d) a bibliographic review of safety data together with an expert report, and where required by the competent authority of the Member State, upon additional request, data necessary for assessing the safety of the herbal medicinal product.

   For the purposes of the first subparagraph, point (c), at the request of the Member State where the application for traditional-use registration has been submitted, the herbal medicinal products working group shall draw up an opinion on the adequacy of the evidence of the long-standing use referred to in the first subparagraph, point (c), of the herbal medicinal product, or of the corresponding herbal medicinal product. The Member State shall submit relevant documentation supporting the referral.

For the purposes of the first subparagraph, point (d), if the individual active substances are not sufficiently known, the data referred to in the first subparagraph, point (a)(iv), shall also relate to the individual active substances.

Annex II shall apply by analogy to the particulars and documentations specified in the first subparagraph, point (a).

2. The requirement to show medicinal use throughout the period of at least 30 years, set out in paragraph 1, first subparagraph, point (c), is satisfied even where the marketing of the herbal medicinal product has not been based on a specific marketing authorisation. It is likewise satisfied where the number or quantity of ingredients of the herbal medicinal product has been reduced during that period.

3. Where the herbal medicinal product has been used in the Union for less than 15 years but is otherwise eligible for a traditional-use registration in accordance with paragraph 1, the competent authority of the Member State where the application for traditional-use registration has been submitted shall refer the application for the traditional herbal medicinal product to the herbal medicinal products working group and submit relevant documentation supporting this referral.

The herbal medicinal products working group shall consider whether the criteria other than the period of transitional use for a traditional-use registration as referred to in Article 134 are complied with. If the herbal medicinal products working group considers it possible, it shall establish a Union herbal monograph as referred to in Article 141(3) which shall be taken into account by the competent authority of Member State when taking its final decision on the application for the traditional use registration.

Article 137

Application of mutual recognition to traditional herbal medicinal products

1. Chapter III, Sections 3 to 5, shall apply by analogy to traditional-use registrations granted in accordance with Article 134, provided that:

   (a) a Union herbal monograph has been established in accordance with Article 141(3); or

   (b) the traditional herbal medicinal product consists of herbal substances, herbal preparations or combinations thereof contained in the list referred to in Article 139.

2. For traditional herbal medicinal products not covered by paragraph 1, the competent authority of each Member State shall, when evaluating an application for traditional-use registration, take due account of registrations granted by the competent authority of another Member State in accordance with this Section.

Article 138

Refusal of registration of traditional herbal medicinal products

1. Traditional-use registration shall be refused if the application does not comply with Articles 134, 135 or 136 or if at least one of the following conditions is fulfilled:

(a) the qualitative or quantitative composition is not as declared;

(b) the therapeutic indications do not comply with the conditions laid down in Article 134;

(c) the traditional herbal medicinal product could be harmful under normal conditions of use;

(d) the data on traditional use are insufficient, especially if pharmacological effects or efficacy are not plausible on the basis of long-standing use and experience;

(e) the pharmaceutical quality is not satisfactorily demonstrated.

2. The competent authorities of the Member States shall notify the applicant, the Commission and any competent authority of the Member State that requests it, of any decision they take to refuse traditional-use registration and the reasons for the refusal.

Article 139

List of herbal substances, herbal preparations and combinations thereof

1. The Commission shall adopt implementing acts to establish a list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products, taking into account the draft list prepared by the herbal medicinal products working group. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 214(2). The list shall contain, with regard to each herbal substance, the therapeutic indication, the specified strength and the posology, the route of administration and any other information necessary for the safe use of the herbal substance as a traditional herbal medicinal product.

2. If an application for traditional-use registration relates to a herbal substance, preparation or a combination thereof contained in the list referred to in paragraph 1, the data specified in Article 136(1), points (b), (c) and (d), shall not be required and Article 138(1), points (c) and (d), shall not apply.

3. If a herbal substance, preparation or a combination is no longer included in the list referred to in paragraph 1, registrations pursuant to paragraph 2 for herbal medicinal products containing this substance shall be revoked unless the particulars and documentations referred to in Article 136(1) are submitted within three months.

Article 140

Other requirements for traditional herbal medicinal products

1. Article 1(5), points (a) and (b) and Article 1(10), point (c), Articles 6 to 8, 29, 30, 44, 46, 90, 155, Article 188, paragraphs 1 and 11, Articles 191, 195, 196, 198, 199(2), 202, 203 and 204 and Chapters IX and XI of this Directive as well as Commission Directive

2003/94/EC[40] shall apply, *mutadis mutandis*, to traditional-use registrations granted under this Section.

2. In addition to the requirements set out in Articles 63 to 66, 70 to 79 and Annex IV, any labelling and package leaflet of a traditional herbal medicinal product shall contain a statement to the effect that:

   (a) the product is a traditional herbal medicinal product for use in specified therapeutic indication(s) exclusively based upon long-standing use; and

   (b) the user should consult a doctor or a qualified healthcare practitioner if the symptoms persist during the use of the traditional herbal medicinal product or if adverse effects not mentioned in the package leaflet occur.

   A Member State may require that the labelling and the package leaflet shall also state the nature of the tradition in question.

3. In addition to the requirements set out in Chapter XIII, any advertisement for a traditional herbal medicinal product registered under this Section shall contain the following statement: Traditional herbal medicinal product for use in specified therapeutic indication(s) exclusively based upon long-standing use.

Article 141

Herbal medicinal products working group

1. A herbal medicinal products working group is established as referred to in Article 142 of [revised Regulation (EC) No 726/2004]. That working group shall be part of the Agency and shall have the following competence:

   (a) as regards traditional-use registrations, to:

      (i) perform the tasks arising from Article 136, paragraphs 1 and 3;

      (ii) perform the tasks arising from Article 137;

      (iii) prepare a draft list of herbal substances, preparations and combinations thereof, as referred to in Article 139(1);

      (iv) establish Union monographs for traditional herbal medicinal products, as referred to in paragraph 3;

   (b) as regards marketing authorisations of herbal medicinal products, to establish Union herbal monographs for herbal medicinal products, as referred to in paragraph 3;

[40] Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (OJ L 262, 14.10.2003, p. 22).

(c) as regards referrals to the Agency under Chapter III, Section 5, or Article 95, in relation to traditional herbal medicinal products as referred to in Article 134, to perform the tasks set out in Article 41;

(d) where a matter concerning medicinal products, other than the traditional-use medicinal products, other medicinal products containing herbal substances is referred to the Agency under Chapter III, Section 5, or Article 95, to give an opinion on the herbal substance, where appropriate.

Appropriate coordination with the Committee for Human Medicinal Products for Human Use shall be ensured by a procedure to be determined by the Executive Director of the Agency in accordance with Article 145(10) of [revised Regulation (EC) No 726/2004].

2. Each Member State shall appoint, for a three-year term which may be renewed, one member and one alternate to the herbal medicinal working group.

The alternates shall represent and vote for the members in their absence. Members and alternates shall be chosen for their role and experience in the evaluation of herbal medicinal products and shall represent the competent authorities of the Member States.

The members of the herbal medicinal products working group may be accompanied by experts in specific scientific or technical fields.

3. The herbal medicinal products working group shall establish Union herbal monographs for herbal medicinal products with regard to the application submitted in accordance with of Article 13 as well as traditional herbal medicinal products.

Where the Union herbal monographs have been established, they shall be taken into account by the competent authorities of Member States when examining an application. Where no such Union herbal monograph has yet been established, other appropriate monographs, publications or data may be referred to.

When new Union herbal monographs are established, the traditional-use registration holder shall consider whether it is necessary to modify the registration dossier accordingly. The traditional-use registration holder shall notify any such modification to the competent authority of the Member State concerned.

The herbal monographs shall be published.

4. Provisions of Article 146, paragraphs 3 to 5 of the [revised Regulation (EC) No 726/2004] applying to the working party shall apply by analogy to herbal medicinal products working group.

5. The herbal medicinal products working group shall draft its rules of procedure.

Chapter XI
Manufacturing and import

SECTION 1

MANUFACTURING AND IMPORT OF MEDICINAL PRODUCTS

Article 142

Manufacturing authorisation

1. Member States shall take all appropriate measures to ensure that the manufacture of the medicinal products within their territory is subject to authorisation (the "manufacturing authorisation"). The manufacturing authorisation shall be required also if the medicinal products manufactured are intended for export.

2. The manufacturing authorisation referred to in paragraph 1 shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging or presentation.

3. By derogation from paragraph 2, the manufacturing authorisation shall not be required for the following:

   (a) preparation, dividing up, changes in packaging or presentation where these processes are carried out, solely for retail supply, by pharmacists in dispensing pharmacies or by persons legally authorised in the Member States to carry out such processes; or

   (b) decentralised sites carrying out manufacturing or testing steps under the responsibility of the qualified person of a central site referred to in Article 151(3).

4. A manufacturing authorisation shall also be required for imports of medicinal products coming from third countries into a Member State.

   This Chapter and Articles 195(5) and 198 shall apply to imports of medicinal products from third countries.

5. Member States shall enter the information relating to the manufacturing authorisation referred to in paragraph 1 in the Union database referred to in Article 188(15).

Article 143

Requirements for a manufacturing authorisation

1. In order to obtain the manufacturing authorisation, the applicant shall submit an application by electronic means to the competent authority of the Member State concerned.

   That application shall include the following particulars:

(a) the medicinal products, the pharmaceutical forms and the manufacturing operations that are to be manufactured, imported or carried out and the place where the activity will take place;

(b) proof that the applicants have at their disposal, for the manufacture or import of the above, suitable and sufficient premises, technical equipment and control facilities complying with the legal requirements that the Member State concerned lays down as regards both manufacture and control and the storage of medicinal products, in accordance with Article 8;

(c) proof that the applicants have at their disposal the services of at least one qualified person within the meaning of Article 151;

(d) explanation on whether the site is the central site responsible for the oversight of decentralised sites.

2. The applicant shall provide, by electronic means, particulars in support of the above in their application.

Article 144

Granting of a manufacturing authorisation

1. The official representatives of the competent authority of the Member State concerned shall carry out an inspection to ensure the accuracy of the particulars included in the application submitted in accordance with Article 143.

Where the accuracy of the particulars is confirmed in accordance with the first subparagraph and no later than 90 days after the receipt of the application submitted in accordance with Article 143, the competent authority of the Member State shall grant or refuse a manufacturing authorisation.

2. To ensure that the particulars referred to in Article 143 are duly submitted, the competent authority of the Member State may grant a manufacturing authorisation subject to conditions.

For central sites, a manufacturing authorisation shall include for each decentralised site a written confirmation that the manufacturer of the medicinal product has verified compliance of the decentralised site with principles of good manufacturing practice referred to in Article 160 by conducting regular audits in accordance with Article 147(1), first subparagraph, point (f).

3. The manufacturing authorisation shall apply only to the medicinal products, pharmaceutical forms, the manufacturing operations and the premises specified in the application and to the premises of the corresponding central site where decentralised manufacturing or testing activities are carried out in decentralised sites, which are registered in accordance with Article 148.

Article 145

Changes in a manufacturing authorisation

If the manufacturing authorisation holder requests a change in any of the particulars referred to in Article 143(1), second subparagraph, the competent authority of the Member State shall amend the manufacturing authorisation no later than 30 days from such request. In exceptional cases this period of time may be extended to 90 days.

Article 146

Request for additional information

The competent authority of the Member State may request the applicant to submit additional information on the particulars supplied pursuant to Article 143(1) and on the qualified person referred to in Article 151; where the competent authority of the Member State makes such request, the time limits referred to in Articles 144(1), second subparagraph, and 145 shall be suspended until the additional information has been supplied.

Article 147

Obligations of the manufacturing authorisation holder

1. Member States shall ensure that manufacturing authorisation holders shall:

(a) have at their disposal the services of staff who comply with the legal requirements existing in the Member State both as regards manufacture and controls;

(b) dispose of the medicinal products that have been granted a marketing authorisation only in accordance with the legislation of the Member States;

(c) give prior notice to the competent authority of the Member State of any changes they may wish to make to any of the particulars provided in accordance to Article 143;

(d) allow the official representatives of the competent authority of the Member State access to their premises and, where sites carry out manufacturing or testing activities in connection with a central site in the decentralised site, to the premises of the central or the decentralised sites at any time;

(e) enable the qualified persons referred to in Article 151 to carry out their duties, where appropriate also in decentralised sites, for example by placing at their disposal all the necessary resources;

(f) comply, in any relevant site and at all times with the principles of good manufacturing practice for medicinal products;

(g) use only active substances that have been manufactured in accordance with good manufacturing practice for active substances and distributed in accordance with good distribution practices for active substances;

(h) inform the competent authority of the Member State and the marketing authorisation holder immediately if they obtain information that medicinal products that come under the scope of their manufacturing authorisation are, or are suspected of being, falsified irrespective of the way the medicinal products were distributed;

(i) verify that the manufacturers, importers or distributors from whom they obtain active substances are registered with the competent authority of the Member State in which they are established; and

(j) verify the authenticity and quality of the active substances and the excipients.

As regards the first subparagraph, point (c), the competent authority of the Member State shall, in any event, be immediately informed if the qualified person referred to in Articles 143(1), point (c), and 151 is replaced unexpectedly.

For the purposes of points (f) and (g), manufacturing authorisation holders shall verify compliance, respectively, by the manufacturer or distributors of active substances with good manufacturing practice and good distribution practices by conducting audits at the manufacturing and distribution sites of the manufacturer and distributors of active substances. Manufacturing authorisation holders shall verify such compliance either by themselves or through an entity acting on their behalf under a contract.

2. The manufacturing authorisation holder shall ensure that the excipients are suitable for use in medicinal products by ascertaining the appropriate good manufacturing practice on the basis of a formalised risk assessment.

3. The manufacturing authorisation holder shall ensure that the appropriate good manufacturing practice ascertained in accordance with paragraph 2, is applied. The manufacturing authorisation holder shall document the measures taken in accordance with paragraphs 1 and 2.

Article 148

Registration and listing process of decentralised sites

1. The manufacturing authorisation holder of the central site shall register all of its decentralised sites in accordance with the provisions of this Article.

2. The manufacturing authorisation holder of the central site shall request the competent authority of the Member State in which the decentralised site is established, to register the decentralised site.

3. The marketing authorisation holder may commence the activity in the decentralised site in connection with the central site only when the decentralised site is registered in the Union database referred to in Article 188(15) and the link is made in the database with the authorisation of the corresponding central site by the competent authority of the Member state where the decentralised site is located.

4. The competent authority of the Member State in which the decentralised site is established, is responsible, in accordance with Article 188, for the supervision of the manufacturing and testing activities carried out in the decentralised site.

5. For the purpose of paragraph 2 the manufacturing authorisation holder of the central site shall submit a registration form that shall include, at least, the following information:

(a) name or corporate name and permanent address of the decentralised site and a proof of establishment in the Union;

(b) the medicinal products that are subject to manufacturing or testing steps in the decentralised site, including the manufacturing or testing activities to be performed for those medicinal products;

(c) particulars regarding the premises of the decentralised site and the technical equipment to carry out the relevant activities;

(d) the reference to the manufacturing authorisation of the central site;

(e) the written confirmation referred to in Article 144(2), second subparagraph, that the manufacturer of the medicinal product has verified compliance of the decentralised site with principles of good manufacturing practice referred to in Article 160 by conducting audits.

6. The competent authority of the Member State supervising the decentralised site pursuant to paragraph 4 may decide to carry out an inspection as referred to in Article 188(1), first subparagraph, point (a). In such cases, that competent authority shall cooperate with the competent authority of the Member State responsible for the supervision of the central site.

7. Following the registration of the decentralised site pursuant to paragraph 2, the manufacturing authorisation holder of the central site shall list the registered decentralised site in the manufacturing authorisation of the central site.

8. The competent authority of the Member State supervising the decentralised site pursuant to paragraph 4 shall cooperate with the relevant authorities responsible for the supervision of the manufacturing or testing activities under other Union acts as regards the following:

(a) the medicinal products that were manufactured in a decentralised site, the testing or manufacturing of which involves using raw material, medicinal products regulated under other relevant Union law, or medicinal products that are intended to be combined with medical devices;

(b) where specific manufacturing or testing activities are applied to the medicinal products containing, consisting or derived from SoHO for which specific manufacturing or testing activities are applied within a decentralised site that is also authorised under [SoHO Regulation].

9. Where relevant, competent authorities of the Member State supervising the central and decentralised sites may liaise with the competent authority of the Member State responsible for the supervision of the marketing authorisation.

Article 149

Conditions related to the safety feature

1. The safety features referred to in Annex IV shall not be removed or covered, either fully or partially, unless the following conditions are fulfilled:

(a) the manufacturing authorisation holder verifies, prior to partly or fully removing or covering those safety features, that the medicinal product concerned is authentic and that it has not been tampered with;

(b) the manufacturing authorisation holder complies with Annex IV by replacing those safety features with safety features that are equivalent as regards the possibility to verify the authenticity, identification and to provide evidence of tampering of the medicinal product. Such replacement shall be conducted without opening the immediate packaging.

Safety features shall be considered equivalent if they:

(i) comply with the requirements set out in the delegated acts adopted pursuant to Article 67(2); and

(ii) are equally effective in enabling the verification of authenticity and identification of medicinal products and in providing evidence of tampering with medicinal products;

(c) the replacement of the safety features is conducted in accordance with applicable good manufacturing practice for medicinal products; and

(d) the replacement of the safety features is subject to supervision by the competent authority of the Member State.

2. Manufacturing authorisation holders, including those performing the activities referred to in paragraph 1, shall be regarded as producers and therefore held liable for damages in the cases and under the conditions set forth in Directive 85/374/EEC.

Article 150

Potentially falsified medicinal products

1. By derogation from Article 1(2), and without prejudice to Chapter XII, Section 1, Member States shall take the necessary measures in order to prevent medicinal products that are introduced into the Union, but are not intended to be placed on the market in the Union, from entering into circulation if there are sufficient grounds to suspect that those products are falsified.

2. Member States shall organise meetings involving patients' and consumers' organisations and, as necessary, Member States' enforcement officers, in order to communicate public information about the actions undertaken in the area of prevention and enforcement to combat the falsification of medicinal products.

3. In order to establish what the necessary measures referred to in paragraph 1 are the Commission is empowered to adopt delegated acts in accordance with Article 215, to supplement paragraph 1 by specifying the criteria to be considered and the verifications to be made when assessing the potential falsified character of medicinal products introduced into the Union but not intended to be placed on the market.

Article 151

Availability of qualified person

1. Member States shall take all appropriate measures to ensure that the manufacturing authorisation holder has permanently and continuously at their disposal the services of at least one qualified person residing and operating in the Union, in accordance with the conditions laid down in Article 152, responsible in particular for carrying out the duties specified in Article 153.

2. A manufacturing authorisation holder who is a natural person and personally fulfils the conditions laid down in Annex III may assume the responsibility referred to in paragraph 1.

3. Where the manufacturing authorisation is granted to a central site specified in the application pursuant to Article 144(3), the qualified person referred to in paragraph 1 shall also be responsible for carrying out the duties specified in Article 153(4) regarding the decentralised sites.

Article 152

Qualification of qualified person

1. Member States shall ensure that the qualified person referred to in Article 151 fulfils the conditions of qualification set out in Annex III.

2. The manufacturing authorisation holder and the qualified person shall ensure that the practical experience acquired is appropriate to the types of products to be certified.

3. The competent authority of the Member State may lay down appropriate administrative procedures to verify that a qualified person referred to in the paragraph 1 fulfils the conditions set out in Annex III.

Article 153

Responsibilities of the qualified person

1. Member States shall take all appropriate measures to ensure that the qualified person referred to in Article 151, without prejudice to their relationship with the manufacturing authorisation holder, are responsible, subject to the procedures referred to in Article 154, for securing:

   (a) in the case of medicinal products manufactured within the Member States concerned, that each production batch of medicinal products has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorisation;

   (b) in the case of medicinal products imported from third countries, irrespective of whether they have been manufactured in the Union that each production batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the

quality of the medicinal products in accordance with the requirements of the marketing authorisation.

The qualified person referred to in Article 151 shall in the case of medicinal products intended to be placed on the Union market, ensure that the safety features referred to in Annex IV have been affixed on the packaging.

The batches of medicinal products that have undergone the controls referred to in the first subparagraph, point (b), in a Member State shall be exempt from those controls if they are marketed in another Member State, accompanied by the control reports signed by the qualified person.

2. In the case of medicinal products imported from a third country, where appropriate arrangements have been made by the Union with the exporting country to ensure that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Union, and to ensure that the controls referred to in paragraph 1, first subparagraph, point (b), have been carried out in the exporting country, the qualified person may be relieved of responsibility for carrying out those controls.

3. In all cases and particularly where the medicinal products are released for sale, the qualified person shall certify in a register or equivalent format provided for that purpose, that each production batch satisfies the provisions of this Article; that register or equivalent format shall be kept up to date during the time when operations are carried out and shall remain at the disposal of the official representatives of the competent authority of the Member State for the period specified in the provisions of the Member State concerned and in any event for at least five years.

4. For the purposes of Article 151(3), the qualified person shall, in addition:

(a) supervise that the manufacturing or testing activities carried out at the decentralised sites comply with principles of relevant good manufacturing practices referred to in Article 160 and conform to the marketing authorisation;

(b) provide a written confirmation as referred to in Article 144(2), second subparagraph;

(c) notify to the competent authority of the Member State where the decentralised site is established, an inventory of the changes that have taken place as regards the information provided in the registration form submitted pursuant to Article 148(5).

Any changes that may have an impact on the quality or safety of the medicinal products that are manufactured or tested at the decentralised site must be notified immediately.

The Commission is empowered to adopt a delegated act in accordance with Article 215 to supplement the first subparagraph, point (c), specifying the notification made by the qualified person.

Article 154

Professional code of conduct

1. Member States shall ensure that the duties of qualified persons referred to in Article 151 are fulfilled, either by means of appropriate administrative measures or by making such persons subject to a professional code of conduct.

2. Member States may provide for the temporary suspension of a qualified person referred to in Article 151 upon the commencement of administrative or disciplinary procedures against that qualified person for failure to fulfil its duties set out in Article 153.

Article 155

Certificate for export of a medicinal product

1. At the request of the manufacturer, the exporter or the competent authorities of an importing third country, Member States shall certify that a manufacturer of medicinal products is in possession of a manufacturing authorisation. When issuing such certificates Member States shall:

   (a) comply with the prevailing administrative arrangements of the World Health Organization;

   (b) for medicinal products intended for export that are already authorised in their territory, supply the summary of product characteristics as approved by them in accordance with Article 43.

2. When the manufacturer is not in possession of a marketing authorisation it shall provide the competent authorities responsible for issuing the certificate referred to in paragraph 1, with a declaration explaining why a marketing authorisation is not available.

SECTION 2

MANUFACTURING, IMPORT AND DISTRIBUTION OF ACTIVE SUBSTANCES

Article 156

Manufacture of active substances

For the purposes of this Directive, manufacture of active substances used in the manufacturing process of a medicinal product shall include both total and partial manufacture or import of an active substance and the various processes of dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or re-labelling, such as are carried out by a distributor of active substances.

Article 157

Registration of importers, manufacturers and distributors of active substances

1. Importers, manufacturers and distributors of active substances who are established in the Union shall register their activity with the competent authority of the Member State in which they are established.

2. The registration form, to be submitted by electronic means, shall include, at least, the following information:

   (a) name or corporate name and permanent address;

   (b) the active substances that are to be imported, manufactured or distributed;

   (c) particulars regarding the premises and the technical equipment for their activity.

3. The persons referred to in paragraph 1 shall submit, by electronic means, the registration form to the competent authority of the Member State at least 60 days prior to the intended commencement of their activity.

4. The competent authority of the Member State may, based on a risk assessment, decide to carry out an inspection. If the competent authority of the Member State notifies the applicant within 60 days of the receipt of the registration form that an inspection will be carried out, the activity shall not begin before the competent authority of the Member State has notified the applicant that they may commence the activity. If within 60 days of the receipt of the registration form the competent authority of the Member State has not notified the applicant that an inspection will be carried out, the applicant may commence the activity.

5. Annually, the persons referred to in paragraph 1 shall communicate, by electronic means, to the competent authority of the Member State an inventory of the changes that have taken place as regards the information provided in the registration form. Any changes that may have an impact on the quality or safety of the active substances that are manufactured, imported or distributed must be notified immediately.

6. The comptetent authority of the Member State shall enter the information provided in accordance with paragraph 2 in the Union database referred to in Article 188(15).

Article 158

Conditions for importing active substances

1. Member States shall take appropriate measures to ensure that the manufacture, import and distribution on their territory of active substances, including active substances that are intended for export, comply with the principles of good manufacturing practice and good distribution practices for active substances specified in the delegated acts adopted in accordance with Article 160.

2. Active substances shall only be imported if the following conditions are fulfilled:

   (a) the active substances have been manufactured in accordance with the principles of good manufacturing practices at least equivalent to those laid down by the Union pursuant to Article160; and

(b) the active substances are accompanied by a written confirmation issued by the competent authority of the exporting third country stating that:

(i) the principles of good manufacturing practices applicable to the manufacturing site manufacturing the exported active substance are at least equivalent to those laid down by the Union pursuant Article 160;

(ii) the manufacturing site concerned is subject to regular, strict and transparent controls and to the effective enforcement of good manufacturing practice, including repeated and unannounced inspections, so as to ensure a protection of public health at least equivalent to that in the Union; and

(iii) in the event of findings relating to non-compliance, information on such findings is supplied by the exporting third country to the Union without undue delay.

3. The conditions set out in paragraph 2, point (b), shall not apply if the exporting country is included in the list referred to in Article 159(2).

4. The conditions set out in paragraph 2, point (b), may be waived by any competent authority of a Member State for a period not exceeding the validity of the certificate of good manufacturing practice issued in accordance with Article 188(13) where a site manufacturing an active substance for export has been inspected by the competent authority of a Member State and was found to comply with the principles of good manufacturing practice laid down pursuant to Article160.

Article 159

Active substances imported from third countries

1. At the request of a third country, the Commission shall assess whether that country's regulatory framework applicable to active substances exported to the Union and the respective control and enforcement activities ensure a level of protection of public health equivalent to that of the Union.

The assessment shall take the form of a review of relevant documentation submitted by electronic means and, unless arrangements as referred to in Article 153(2) are in place that cover this area of activity, that assessment shall include an on-site review of the third country's regulatory system and, if necessary, an observed inspection of one or more of the third country's manufacturing sites for active substances.

2. Based on the assessment referred to in paragraph 1, the Commission may adopt implementing acts to include the third country in a list and to apply the requirements set out in the second subparagraph. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 214(2).

When assessing the third country pursuant to paragraph 1, the Commission shall take account of the following:

(a) the country's rules for good manufacturing practice;

(b) the regularity of inspections to verify compliance with good manufacturing practice;

(c) the effectiveness of enforcement of good manufacturing practice;

(d) the regularity and rapidity of information provided by the third country relating to non-compliant manufacturers of active substances.

3. The Commission shall verify regularly whether the conditions laid down in paragraph 1 are fulfilled. The first verification shall take place no later than 3 years after the third country has been included in the list referred to in paragraph 2.

4. The Commission shall perform the assessment referred to in pargarph 1 and verification referred to in paragraph 3 in cooperation with the Agency and the competent authorities of the Member States.

SECTION 3

PRINCIPLES OF GOOD MANUFACTURING AND GOOD DISTRIBUTION PRACTICES

Article 160

Rules applicable to medicinal products and active substances

The Commission may adopt implementing acts in accordance with Article 214(2) to supplement this Directive by specifying:

(a) the principles of good manufacturing and good distribution practices for medicinal products complemented, where relevant, by specific measures applicable notably to pharmaceutical forms, medicinal products or manufacturing activities in line with good manufacturing principles;

(b) the principles of good manufacturing and good distribution practices for active substances.

Where relevant, these principles shall be specified in coherence with any principles of good practices established under any other Union legal framework.

Article 161

Rules applicable to excipients

The Commission is empowered to adopt delegated acts in accordance with Article 215 to supplement this Directive on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients referred to in Article 147(2). Such risk assessment shall take into account requirements under other appropriate quality systems as well as the source and intended use of the excipients and previous instances of quality defects.

Chapter XII
Wholesale distribution and sale at a distance

SECTION 1

WHOLESALE DISTRIBUTION AND BROKERING OF MEDICINAL PRODUCTS

Article 162

Wholesale distribution of medicinal products

1. Without prejudice to Article 5, Member States shall take all appropriate action to ensure that only medicinal products in respect of which a marketing authorisation has been granted in accordance with Union law are distributed on their territory.

2. In the case of wholesale distribution including storage, medicinal products shall be covered by either a centralised marketing authorisation or by a national marketing authorisation.

3. Distributors who intend to import a medicinal product from another Member State shall notify the marketing authorisation holder and the competent authority of the Member State to which the medicinal product is to be imported of their intention to import that medicinal product.

4. In the case of medicinal products covered by a national marketing authorisation, the notification referred to in paragraph 3 to the competent authority of the Member State shall be without prejudice to additional procedures provided for in the legislation of that Member State and to fees payable to the competent authority of the Member State for examining the notification.

5. In the case of medicinal products covered by a centralised marketing authorisation, the distributor shall submit the same notification referred to in paragraph 3 to the Agency which will be in charge of checking that the conditions laid down in Union law on medicinal products and in the marketing authorisations are observed. For this check, a fee shall be payable to the Agency.

Article 163

Authorisation for wholesale distribution of medicinal products

1. The competent authority of the Member State concerned shall take all appropriate measures to ensure that the wholesale distribution of medicinal products is subject to an authorisation to engage in activity as a wholesaler in medicinal products ("wholesale distribution authorisation"). The wholesale distribution authorisation shall indicate the premises, the medicinal products and the wholesale distribution operations for which it is valid.

2. Where persons authorised or entitled to supply medicinal products to the public may also, under national law, engage in wholesale business, such persons shall be subject to the authorisation provided for in paragraph 1.

3. A manufacturing authorisation required under Article 142 shall include an authorisation to distribute by wholesale the medicinal products that it covers. A wholesale distribution authorisation shall not give dispensation from the obligation set out in Article 142 to hold a manufacturing authorisation and to comply with the conditions set out in that respect, even where the manufacturing or import business is secondary.

4. The competent authority of the Member State concerned shall enter the information relating to the wholesale distribution authorisations in the Union database referred to in Article 188(15).

5. The competent authority of the Member State that granted the wholesale distribution authorisation for premises located in its territory shall ensure that controls of the persons authorised to engage in activity as a wholesaler in medicinal products, and inspections of their premises, are carried out at an appropriate frequency.

   The competent authority of the Member State that granted the wholesale distribution authorisation shall suspend or revoke it if the conditions for granting it set out in Article 162 cease to be met. In such event the Member State shall without undue delay inform the other Member States and the Commission thereof.

6. Where a competent authority of a Member State considers that the conditions for granting a wholesale distribution authorisation set out in Article 162 are not met with respect to a wholesale distribution authorisation granted by the competent authority of another Member State, it shall without undue delay inform the Commission and the competent authority of the other Member State thereof. The competent authority of the other Member State shall take the measures it considers necessary and shall inform the Commission and the competent authority of the first Member State of those measures and the reasons for them.

Article 164

Requirements for a wholesale distribution authorisation

1. In order to obtain a wholesale distribution authorisation, applicants shall submit an application by electronic means to the competent authority of the Member State concerned.

2. The application referred to in paragraph 1 shall include the following particulars:

   (a) a confirmation and proof that the applicants have at their disposal suitable and adequate premises, installations and equipment, to ensure proper conservation and distribution of the medicinal products;

   (b) a confirmation and proof that the applicants have at their disposal appropriately trained staff, and in particular, a qualified person designated as responsible, meeting the conditions provided for by the legislation of the Member State concerned;

   (c) an undertaking to fulfil the obligations incumbent on them under the terms of Article 166.

Article 165

Granting of a wholesale distribution authorisation

1. The official representatives of the competent authority of the Member State concerned shall carry out an inspection to confirm the accuracy of the particulars provided in accordance with Article 164.

   Where the accuracy of the particulars is confirmed in accordance with the first subparagraph and no later than 90 days after the receipt of the application submitted in accordance with Article164, the competent authority of the Member State shall grant or refuse a wholesale distribution authorisation.

2. The competent authority of the Member State concerned may require the applicant to supply, by electronic means, all necessary information concerning the particulars for granting the wholesale distribution authorisation. In such case, the period laid down in paragraph 1 shall be suspended until the requisite additional information is supplied.

3. The competent authority of the Member State may grant a wholesale distribution authorisation subject to conditions.

4. The wholesale distribution authorisation shall apply only to the premises specified in the authorisation.

Article 166

Obligations of the wholesale distribution authorisation holder

1. Member States shall ensure that wholesale distribution authorisation holders shall:

   (a) have at their disposal the services of staff who comply with the legal requirements existing in the Member State as regards wholesale distribution;

   (b) allow the official representatives of the competent authority of the Member State access to their premises, installations and equipment referred to in Article 164(2), point (a), at all times;

   (c) obtain, including by financial transactions, their supplies of medicinal products only from persons who are themselves in possession of a wholesale distribution authorisation in the Union or a manufacturing authorisation referred to in Article 163(3);

   (d) supply, including by financial transaction, medicinal products only to persons who are themselves wholesale distribution authorisation holders or who are authorised or entitled to supply medicinal products to the public;

   (e) verify that the medicinal products received are not falsified by checking the safety features on the outer packaging, in accordance with the requirements laid down in the delegated acts adopted pursuant to Article 67(2), second subparagraph;

(f) have an emergency plan that ensures effective implementation of any recall from the market ordered by the competent authorities or carried out in cooperation with the manufacturer or marketing authorisation holder for the medicinal product concerned;

(g) keep records giving, for any medicinal products received, dispatched or brokered, at least the following information:

(i) the date of receipt, dispatch or brokering of the medicinal product,

(ii) the name of the medicinal product,

(iii) the quantity of the medicinal product received, supplied or brokered,

(iv) the name and address of the supplier of the medicinal product or the consignee, as appropriate,

(v) the batch number of the medicinal products, at least for medicinal products bearing the safety features referred to in Article 67;

(h) keep the records referred to in point (g) available to the competent authorities of the Member States, for inspection purposes, for a period of five years;

(i) comply with the principles of good distribution practices for medicinal products laid down in Article 160;

(j) maintain a quality system setting out responsibilities, processes and risk management measures in relation to their activities;

(k) immediately inform the competent authority of the Member State and, where applicable, the marketing authorisation holder, of medicinal products they receive or are offered that they identify as falsified or suspect to be falsified;

(l) continuously guarantee the appropriate and continued supply of an adequate range of medicinal products to meet the requirements of a specific geographical area, and deliver the supplies requested over the whole of the area in question, within a reasonable timeframe, which shall be defined in the national legislation;

(m) cooperate with marketing authorisation holders and competent authorities of the Member States on the security of supply.

2. Where the medicinal product is obtained from another wholesale distributor, the wholesale distribution authorisation holders obtaining the product shall verify compliance with the principles of good distribution practices by the supplying wholesale distributor. This includes verifying whether the supplying wholesale distributor holds a wholesale distribution authorisation, or a manufacturing authorisation referred to in Article 163(3).

3. Where the medicinal product is obtained from a manufacturer or importer, wholesale distribution authorisation holders shall verify that the manufacturer or importer holds a manufacturing authorisation.

4. Where the medicinal product is obtained through brokering of medicinal products, wholesale distribution authorisation holders shall verify that the person brokering the medicinal product fulfils the requirements set out in Article 171.

Article 167

Obligation of supply of medicinal products

1. With regard to the supply of medicinal products to pharmacists and persons authorised or entitled to supply medicinal products to the public, Member States shall not impose upon the wholesale distribution authorisation holder that has been granted by another Member State any obligation, in particular public service obligations, more stringent than those they impose on persons whom they have themselves authorised to engage in equivalent activities.

2. The wholesale distributors of a medicinal product placed on the market in a Member State shall, within the limits of their responsibilities, ensure appropriate and continued supplies of that medicinal product to pharmacies and persons authorised to supply medicinal products so that the needs of patients in the Member State in question are covered.

3. The arrangements for implementing this Article should, moreover, be justified on grounds of public health protection and be proportionate in relation to the objective of such protection, in compliance with the Treaty rules, particularly those concerning the free movement of goods and competition.

Article 168

Documentation accompanying supplied medicinal products

1. For all supplies of medicinal products to a person authorised or entitled to supply medicinal products to the public in the Member State concerned, the authorised wholesaler must enclose a document that makes it possible to ascertain the following:

   (a) the date of the supply;

   (b) the name and pharmaceutical form of the medicinal product;

   (c) the quantity of the medicinal product supplied;

   (d) the name and address of the supplier of the medicinal product and consignee;

   (e) the batch number of the medicinal products at least for products bearing the safety features referred to in Article 67.

2. Member States shall take all appropriate measures to ensure that persons authorised or entitled to supply medicinal products to the public are able to provide information that makes it possible to trace the distribution path of every medicinal product.

Article 169

National requirements on wholesale distribution

The provisions of this Chapter shall not prevent the application of more stringent requirements laid down by Member States in respect of the wholesale distribution of:

(a) narcotic or psychotropic substances;

(b) medicinal products derived from blood;

(c) immunological medicinal products; and

(d) radiopharmaceuticals.

Article 170

Wholesale distribution to third countries

In the case of wholesale distribution of medicinal products to third countries, Articles 162 and 166(1), point (c), shall not apply.

Where wholesale distributors supply medicinal products to persons in third countries, they shall ensure that such supplies are only made to persons who are authorised or entitled to receive medicinal products for wholesale distribution or supply to the public in accordance with the applicable legal and administrative provisions of the third country concerned.

Article 168 shall apply to the supply of medicinal products to persons in third countries authorised or entitled to supply medicinal products to the public.

Article 171

Brokering medicinal products

1. Persons brokering medicinal products shall ensure that the brokered medicinal products are covered by a valid marketing authorisation.

   Persons brokering medicinal products shall have a permanent address and contact details in the Union, so as to ensure accurate identification, location, communication and supervision of their activities by competent authorities of the Member States.

   The requirements set out in Article 166(1), points (e) to (j), shall apply *mutatis mutandis* to the brokering of medicinal products.

2. Persons may only broker medicinal products if they are registered with the competent authority of the Member State where they have their permanent address referred to in paragraph 1, second subparagraph. Those persons shall submit, by electronic means, at least, their name, corporate name and permanent address to the competent authority in order to register. They shall notify, by electronic means, the competent authority of the Member State of any changes thereof without delay.

   The competent authority of the Member State shall enter the information referred to in the first subparagraph in a register that shall be publicly available.

3. The principles referred to in Article 160 shall include specific provisions for brokering.

4. Inspections referred to in Article 188 shall be carried out under the responsibility of the Member State where the person brokering medicinal products is registered.

If a person brokering medicinal products does not comply with the requirements set out in this Article, the competent authority of the Member State may decide to remove that person from the register referred to in paragraph 2. In such event, the competent authority of the Member State shall notify that person thereof.

SECTION 2

SALE AT A DISTANCE TO THE PUBLIC

Article 172

General requirements for sale at distance

1. Without prejudice to national legislation prohibiting the offer for sale at a distance of prescription medicinal products to the public by means of information society services, Member States shall ensure that medicinal products are offered for sale at a distance to the public by means of services as defined in Directive (EU) 2015/1535 of the European Parliament and of the Council[41] laying down a procedure for the provision of information in the field of technical regulations and of rules on Information Society services under the following conditions:

   (a) the natural or legal person offering the medicinal products is authorised or entitled to supply medicinal products to the public, also at a distance, in accordance with national legislation of the Member State in which that person is established;

   (b) the person referred to in point (a) has notified the Member State in which that person is established of at least the following information:

      (i) name or corporate name and permanent address of the place of activity from where those medicinal products are supplied;

      (ii) the starting date of the activity of offering medicinal products for sale at a distance to the public by means of information society services;

      (iii) the address of the website used for that purpose and all relevant information necessary to identify that website;

      (iv) if applicable, the prescription status in accordance with Chapter IV of the medicinal products offered for sale at a distance to the public by means of information society services.

      Where appropriate, that information shall be updated;

   (c) the medicinal products comply with the national legislation of the Member State of destination in accordance with Article 5(1);

[41] Directive (EU) 2015/1535 of the European Parliament and of the Council of 9 September 2015 laying down a procedure for the provision of information in the field of technical regulations and of rules on Information Society services (OJ L 241, 17.9.2015, p. 1).

(d) without prejudice to the information requirements set out in Directive 2000/31/EC of the European Parliament and of the Council[42], the website offering the medicinal products contains at least:

(i) the contact details of the competent authority of the Member State or the authority notified pursuant to point (b);

(ii) a hyperlink to the website referred to in Article 174 of the Member State of establishment;

(iii) the common logo referred to in Article 173 clearly displayed on every page of the website that relates to the offer for sale at a distance to the public of medicinal products. The common logo shall contain a hyperlink to the entry of the person in the list referred to in Article 174(1), point (c).

2. Member States may impose conditions, justified on grounds of public health protection, for the retail supply on their territory of medicinal products for sale at a distance to the public by means of information society services.

3. Without prejudice to Directive 2000/31/EC and the requirements set out in this Section, Member States shall take the necessary measures to ensure that other persons than those referred to in paragraph 1 that offer medicinal products for sale at a distance to the public by means of information society services and that operate on their territory are subject to effective, proportionate and dissuasive penalties.

Article 173

Requirements for common logo

1. A common logo shall be established that is recognisable throughout the Union, while enabling the identification of the Member State where the person offering medicinal products for sale at a distance to the public is established. That logo shall be clearly displayed on websites offering medicinal products for sale at a distance to the public in accordance with Article 172(1), point (d).

2. In order to harmonise the functioning of the common logo, the Commission shall adopt implementing acts regarding:

(a) the technical, electronic and cryptographic requirements for verification of the authenticity of the common logo;

(b) the design of the common logo.

Those implementing acts shall, where necessary, be amended to take account of technical and scientific progress. Those implementing acts shall be adopted in accordance with the procedure referred to in Article 214(2).

[42] Directive 2000/31/EC of the European Parliament and of the Council of 8 June 2000 on certain legal aspects of information society services, in particular electronic commerce, in the Internal Market (Directive on electronic commerce (OJ L 178, 17.7.2000, p. 1).

Article 174

Information about the supply at distance to the public

1. Each Member State shall set up a website providing at least the following:

   (a) information on the national legislation applicable to the offering of medicinal products for sale at a distance to the public by means of information society services, including information on the fact that there may be differences between Member States regarding classification of medicinal products and the conditions for their supply;

   (b) information on the purpose of the common logo;

   (c) the list of persons offering the medicinal products for sale at a distance to the public by means of information society services in accordance with Article 172 as well as their website addresses;

   (d) background information on the risks related to medicinal products supplied illegally to the public by means of information society services.

   This website shall contain a hyperlink to the website referred to in paragraph 2.

2. The Agency shall set up a website providing the information referred to in paragraph 1, first subparagraph, points (b) and (d), information on the Union law applicable to falsified medicinal products as well as hyperlinks to the websites of the Member States referred to in paragraph 1. The Agency's website shall explicitly mention that the Member States' websites contain information on persons authorised or entitled to supply medicinal products by sales at a distance in the Member State concerned.

3. The Commission shall, in cooperation with the competent authorities, conduct or promote information campaigns aimed at the general public on the dangers of falsified medicinal products. Those campaigns shall raise consumer awareness of the risks related to medicinal products supplied illegally by sales at a distance as well as of the functioning of the common logo and the websites referred to in paragraphs 1 and 2.

Chapter XIII
Advertising

Article 175

Definition of advertising of medicinal products

1. For the purposes of this Chapter, 'advertising of medicinal products' shall include any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products.

   It shall include in particular:

   (a) the advertising of medicinal products to the general public;

(b) advertising of medicinal products to persons qualified to prescribe, administer or supply them;

(c) visits by medical sales representatives to persons qualified to prescribe medicinal products;

(d) the supply of samples of medicinal products;

(e) the provision of inducements to prescribe or supply medicinal products by the gift, offer or promise of any benefit or bonus, whether in money or in kind, except when their intrinsic value is minimal;

(f) sponsorship of promotional meetings attended by persons qualified to prescribe or supply medicinal products;

(g) sponsorship of scientific congresses attended by persons qualified to prescribe or supply medicinal products and in particular payment of their travelling and accommodation expenses in connection therewith;

(h) advertising related to medicinal products, that does not refer to specific medicinal products.

2. The following are not covered by this Chapter:

(a) the labelling and package leaflets, which are subject to the provisions of Chapter VI;

(b) correspondence, possibly accompanied by material of a non-promotional nature, needed to answer a specific question about a particular medicinal product;

(c) factual, informative announcements and reference material relating, for example, to pack changes, adverse-reaction warnings as part of general drug precautions, trade catalogues and price lists, provided they include no product claims;

(d) information relating to human health or diseases, provided that there is no reference, even indirect, to medicinal products.

Article 176

General provisions on advertising of medicinal products

1. Member States shall prohibit any advertising of a medicinal product in respect of which a marketing authorisation has not been granted.

2. All parts of the advertising of a medicinal product must comply with the particulars listed in the summary of product characteristics.

3. The advertising of a medicinal product:

(a) shall encourage the rational use of the medicinal product, by presenting it objectively and without exaggerating its properties;

(b) shall be accurate, verifiable and not be misleading.

4. Any form of advertising that aims to highlight negatively another medicinal product shall be prohibited. Advertising that suggests that a medicinal product is safer or more effective than another medicinal product shall also be prohibited, unless demonstrated and supported by the summary of product characteristics.

Article 177

Restrictions on advertising of medicinal products

1. Member States shall prohibit the advertising to the general public of medicinal products that:

   (a) are available on medical prescription only, in accordance with Chapter IV;

   (b) contain substances classified as psychotropic or narcotic within the meaning of international conventions.

2. Medicinal products may be advertised to the general public where, by virtue of their composition and purpose, they are intended and designed for use without the intervention of a medical practitioner for diagnostic purposes or for the prescription or monitoring of treatment, with the advice of the pharmacist, if necessary.

3. Member States shall be entitled to ban, on their territory, advertising to the general public of medicinal products the cost of which may be reimbursed.

4. The prohibition contained in paragraph 1 shall not apply to vaccination campaigns carried out by the industry and approved by the competent authorities of the Member States.

5. The prohibition referred to in paragraph 1 shall apply without prejudice to Article 21 of Directive 2010/13/EU.

6. Member States shall prohibit the direct distribution of medicinal products to the public by the industry for promotional purposes.

Article 178

Advertising to the general public

1. Without prejudice to Article 177, all advertising to the general public of a medicinal product shall:

   (a) be set out in such a way that it is clear that the message is an advertisement and that the product is clearly identified as a medicinal product;

   (b) include the following minimum information:

      (i) the name of the medicinal product, as well as the common name if the medicinal product contains only one active substance;

      (ii) the information necessary for correct use of the medicinal product;

(iii) an express, legible invitation to read carefully the instructions on the package leaflet or on the outer packaging, as the case may be.

2. Member States may decide that the advertising of a medicinal product to the general public may, notwithstanding paragraph 1, include only the name of the medicinal product or its active substance, or the trademark if it is intended solely as a reminder.

Article 179

Restrictions on advertising to the general public

1. The advertising of a medicinal product to the general public shall not contain any material that:

(a) gives the impression that a medical consultation or surgical operation is unnecessary, in particular by offering a diagnosis or by suggesting treatment by mail;

(b) suggests that the effects of taking the medicinal product are guaranteed, are unaccompanied by adverse reactions or are better than, or equivalent to, those of another treatment or medicinal product;

(c) suggests that the health of the subject can be enhanced by taking the medicinal product;

(d) suggests that the health of the subject could be affected by not taking the medicinal product;

(e) is directed exclusively or principally at children;

(f) refers to a recommendation by scientists, healthcare professionals or persons who are neither of the foregoing but who, because of their celebrity, could encourage the consumption of medicinal products;

(g) suggests that the medicinal product is a food, cosmetic or other consumer product;

(h) suggests that the safety or efficacy of the medicinal product is due to the fact that it is natural;

(i) could, by a description or detailed representation of a case history, lead to erroneous self-diagnosis;

(j) refers, in improper, alarming or misleading terms, to claims of recovery;

(k) uses, in improper, alarming or misleading terms, pictorial representations of changes in the human body caused by disease or injury, or of the action of a medicinal product on the human body or parts thereof.

2. The prohibition set out in the paragraph 1, point (d), shall not apply to the vaccination campaigns referred to in Article 177(4).

Article 180

Advertising to persons qualified to prescribe, administer or supply medicinal products

1. Any advertising of a medicinal product to persons qualified to prescribe, administer or supply such products shall include:

   (a) essential information compatible with the summary of product characteristics;

   (b) the supply prescription status of the medicinal product.

   Member States may also require such advertising to include the selling price or indicative price of the various presentations and the conditions for reimbursement by social security bodies.

2. Member States may decide that the advertising of a medicinal product to persons qualified to prescribe, administer or supply such products may, notwithstanding paragraph 1, include only the name of the medicinal product, or its international non-proprietary name, where this exists, or the trademark, if it is intended solely as a reminder.

Article 181

Supporting documentation for advertising to persons qualified to prescribe, administer or supply medicinal products

1. Any documentation relating to a medicinal product that is transmitted as part of the promotion of that medicinal product to persons qualified to prescribe, administer or supply it shall include, as a minimum, the particulars listed in Article 180(1) and shall state the date on which it was drawn up or last revised.

2. All the information contained in the documentation referred to in paragraph 1 shall be accurate, up-to-date, verifiable and sufficiently complete to enable the recipient to form their own opinion of the therapeutic value of the medicinal product concerned.

3. Quotations as well as tables and other illustrative matter taken from medical journals or other scientific works for use in the documentation referred to in paragraph 1 shall be faithfully reproduced and the precise sources indicated.

Article 182

Obligations related to medical sales representatives

1. Medical sales representatives shall be given adequate training by the undertaking that employs them and shall have sufficient scientific knowledge to be able to provide information that is precise and as complete as possible about the medicinal products that they promote. The information provided by medical sales representatives shall be in accordance with Article 176.

2. During each visit, medical sales representatives shall give the persons visited, or have available for them, summaries of the product characteristics of each medicinal product they

present together, if the legislation of the Member State so permits, with details of the price and conditions for reimbursement referred to in Article 180(1), second subparagraph.

3. Medical sales representatives shall transmit to the scientific service referred to in Article 187(1) any information about the use of the medicinal products they advertise, with particular reference to any adverse reactions reported to them by the persons they visit.

Article 183

Promotion of medicinal products

1. Where medicinal products are being promoted to persons qualified to prescribe or supply them, no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to such persons unless they are inexpensive and relevant to the practice of medicine or pharmacy.

2. Hospitality at sales promotion events shall always be strictly limited to their main purpose and must not be extended to persons other than persons qualified to prescribe or supply medicinal products.

3. Persons qualified to prescribe or supply medicinal products shall not solicit or accept any inducement prohibited under paragraph 1 or contrary to paragraph 2.

4. Existing measures or trade practices in Member States relating to prices, margins and discounts shall not be affected by the rules set out in paragraphs 1, 2 and 3.

Article 184

Hospitality at scientific events

The provisions of Article 183(1) shall not prevent hospitality being offered, directly or indirectly, at events for purely professional and scientific purposes. Such hospitality shall always be strictly limited to the main scientific objective of the event. It must not be extended to persons other than persons qualified to prescribe or supply medicinal products.

Article 185

Provision of samples of medicinal products

1. Free samples of medicinal products shall be provided on an exceptional basis only to persons qualified to prescribe them and on the following conditions:

   (a) the number of samples for each medicinal product each year on prescription shall be limited;

   (b) any supply of samples shall be in response to a written request, signed and dated, from the persons qualified to prescribe or supply medicinal products;

   (c) the persons qualified to supply samples shall maintain an adequate system of control and accountability;

(d) each sample shall be no larger than the smallest presentation on the market;

(e) each sample shall be marked 'free medical sample — not for sale' or shall show some other wording having the same meaning;

(f) each sample shall be accompanied by a copy of the summary of product characteristics;

(g) no samples of medicinal products containing substances classified as psychotropic or narcotic within the meaning of international conventions may be supplied.

2. On an exceptional basis, free samples of medicinal products not subject to medical prescription may also be provided to persons qualified to supply them, subject to the conditions of paragraph 1.

3. Member States may also place further restrictions on the distribution of samples of certain medicinal products.

Article 186

Implementation of advertising provisions by the Member States

1. Member States shall ensure that there are adequate and effective methods to monitor the advertising of medicinal products. Such methods, which may be based on a system of prior vetting, shall in any event include legal provisions under which persons or organisations regarded under national law as having a legitimate interest in prohibiting any advertisement inconsistent with this Chapter, may take legal action against such advertisement, or bring such advertisement before the competent authority of the Member State either to decide on complaints or to initiate appropriate legal proceedings.

2. Under the legal provisions referred to in paragraph 1, Member States shall confer upon the courts or competent authorities of the Member States powers enabling them, in cases where they deem such measures to be necessary, taking into account all the interests involved, and in particular the public interest:

(a) to order the cessation of, or to institute appropriate legal proceedings for an order for the cessation of, misleading advertising; or

(b) if misleading advertising has not yet been published but publication is imminent, to order the prohibition of, or to institute appropriate legal proceedings for an order for the prohibition of, such publication.

Member States shall confer upon the courts or competent authorities of the Member States the powers referred to in the first subparagraph, points (a) and (b), even without proof of actual loss or damage or of intention or negligence on the part of the advertiser.

3. Member States shall make provision for the measures referred to in paragraph 2 to be taken under an accelerated procedure, either with interim effect or with definitive effect.

It shall be for each Member State to decide which of the two options set out in the first subparagraph to select.

4. Member States may confer upon the courts or competent authorities of the Member States powers enabling them, with a view to eliminating the continuing effects of misleading advertising the cessation of which has been ordered by a final decision:

(a) to require publication of that decision in full or in part and in such form as they deem adequate;

(b) to require in addition the publication of a corrective statement.

5. The paragraphs 1 to 4 shall not exclude the voluntary control of advertising of medicinal products by self-regulatory bodies and recourse to such bodies, if proceedings before such bodies are possible in addition to the judicial or administrative proceedings referred to in paragraph 1.

Article 187

Implementation of advertising provisions by the marketing authorisation holder

1. The marketing authorisation holders shall establish, within their undertaking or not-for-profit entities, a scientific service in charge of information about the medicinal products that they place on the market.

2. The marketing authorisation holder shall:

(a) keep available for, or communicate to, the competent authorities of the Member States or bodies responsible for monitoring advertising of medicinal products, a sample of all advertisements emanating from its undertaking or not-for-profit entities together with a statement indicating the persons to whom it is addressed, the method of dissemination and the date of first dissemination;

(b) ensure that advertising of medicinal products by their undertaking or not-for-profit entities conforms to the requirements of this Chapter;

(c) verify that medical sales representatives employed by their undertaking or not-for-profit entities have been adequately trained and fulfil the obligations imposed upon them by Article 182, paragraphs 2 and 3;

(d) supply the competent authorities of the Member States or bodies responsible for monitoring advertising of medicinal products with the information and assistance they require to carry out their responsibilities;

(e) ensure that the decisions taken by the competent authorities of the Member States or bodies responsible for monitoring advertising of medicinal products are immediately and fully complied with.

3. The Member States shall not prohibit the co-promotion of a medicinal product by the marketing authorisation holders and one or more companies nominated by them.

Chapter XIV
Supervision and controls

SECTION 1

SUPERVISION

Article 188

System of supervision and inspections

1. The competent authority of the Member State concerned shall, in cooperation with the Agency and where relevant, other Member States, ensure compliance with the rules of this Directive, namely the principles of good manufacturing practice and good distribution practices referred to in Articles 160 and 161.

   For the purposes of the first subparagraph, the competent authority of the Member State shall have in place a system of supervision that shall include the following measures:

   (a) announced and, where appropriate, unannounced on-site inspections;

   (b) remote inspections, where justified;

   (c) compliance control measures;

   (d) the effective follow-up of the measures referred to in points (a), (b) and (c).

2. The competent authorities of the Member State concerned, and the Agency shall exchange information on the inspections referred to in paragraph 1, second subparagraph, points (a) and (b), that are planned or that have been conducted and shall cooperate in the coordination of such inspections.

3. The competent authority of the Member State shall ensure that the measures referred to in paragraph 1, second subparagraph, are carried out by the official representatives of the competent authority of the Member State:

   (a) at an appropriate frequency based on risk, at the premises or on the activities of manufacturers of medicinal products, located in the Union or in third countries, including where appropriate at central or decentralised site(s), and at the premises or on the activities of wholesale distributors of medicinal products located in the Union;

   (b) at an appropriate frequency based on risk, at the premises or on the activities of the manufacturers of active substances located in the Union or in third countries and at the premises or on the activities of importers, or distributors of active substances, located in the Union.

4. To determine the appropriate frequency based on risk referred to in paragraph 3, point (b), the competent authority of the Member State may:

(a) rely on inspection reports from trusted non-Union regulatory authorities;

(b) take into account whether the manufacturer of active substance is located in a third country included in the list referred to in Article 159(2).

5. Where the competent authority of the Member State considers it necessary, in particular where there are grounds for suspecting non-compliance with the rules of this Directive, including with the principles of good manufacturing practice and good distribution practices, referred to in Articles 160 and 161, it may have its official representatives carry out the measures referred to in paragraph 1, second subparagraph at the premises or on the activities of:

(a) manufacturers or importers of medicinal products applying for a manufacturing import authorisation or wholesale distributors applying for a wholesale distribution authorisation;

(b) manufacturers of active substance applying for a registration or manufacturing sites applying for a registration as decentralised sites;

(c) marketing authorisation holders;

(d) distributors of medicinal products or active substances located in third countries;

(e) manufacturers of excipients, functional excipients, starting materials or intermediate products located in its territory or in a third country;

(f) importers of excipients, functional excipients, starting materials or intermediate products located in its territory;

(g) persons brokering medicinal products located in its territory.

6. The measures referred to in paragraph 1, second subparagraph, may also be carried out at the request of a competent authority of a Member State, the Commission or the Agency in the Union or in third countries or, where appropriate, by asking an Official Medicines Control Laboratory or a laboratory that Member State has designated for that purpose to carry out tests on samples.

7. Each Member State shall ensure that official representatives of its competent authorities are empowered and required to carry out one or more of the following activities:

(a) inspect the manufacturing or commercial establishments of manufacturers of medicinal products, of active substances or of excipients, and any laboratories employed by the manufacturing authorisation holder to carry out verifications and controls pursuant to Article 8;

(b) take samples during an inspection or request samples as part of the measures referred to in paragraph 1, second subparagraph, including any required essential testing material or reagent with a view to independent tests being carried out by an Official Medicines Control Laboratory or a laboratory that a Member States has designated for that purpose;

(c) inspect the premises, records, documents and pharmacovigilance system master file of the marketing authorisation holder or any undertaking employed by the marketing authorisation holder to perform the activities described in Chapter IX.

8. Inspections referred to in paragraph 1, second subparagraph, points (a) and (b), shall be carried out in accordance with the principles referred to in Article 190.

9. After every inspection carried out in accordance with paragraphs 3 and 5, the competent authority of the Member State concerned shall issue a report on the compliance of the manufacturing activities inspected with the good manufacturing practice and good distribution practices referred to in Articles 160 and 161, as applicable.

10. The competent authority of the Member State that had its official representatives carry out inspections in accordance with paragraphs 3 and 5, shall share its draft report with the inspected entity.

11. Before adopting the report, the competent authority of the Member State shall give the inspected entity the opportunity to submit comments.

12. Without prejudice to any arrangements that may have been concluded between the Union and third countries, a Member State, the Commission or the Agency may require a manufacturer of a medicinal product or of an active substance established in a third country to submit to an inspection as referred to in this Article.

13. Within 90 days of the conclusion of an inspection carried out in accordace with paragraphs 3 and 5 the competent authority of the Member State concerned shall issue to the inspected entity a certificate of compliance of good manufacturing practice or good distribution practices if the outcome of that inspection shows that the inspected entity complies with the principles of good manufacturing practice or good distribution practices referred to in Articles 160 and 161.

14. If the outcome of the inspection carried out in accordance with paragraph 3, 4 and 5 shows that the inspected entity does not comply with the principles of good manufacturing practice or good distribution practices as referred to in Articles 160 and 161, the competent authority of the Member State concerned shall issue a statement of non-compliance.

15. The competent authority of the Member State shall enter the certificates of good manufacturing practice or good distribution practices in the relevant Union database managed by the Agency on behalf of the Union. Pursuant to Article 157, the competent authority of the Member States shall also enter information in that database regarding the registration of importers, manufacturers and distributors of active substances and decentralised sites performing decentralised manufacturing activities, including their respective database link to the manufacturing authorisation of the central site.

16. If the outcome of the inspection carried out in accordance with paragraph 5 is that the inspected entity does not comply with the legal requirements or the principles of good manufacturing practice or good distribution practices as referred to in Articles 160 and 161 the information shall be entered in the Union database as referred to in paragraph 15.

17. If the outcome of the activity carried out in accordance with paragraph 7, point (c), is that the marketing authorisation holder does not comply with the pharmacovigilance system as described in the pharmacovigilance system master file and with Chapter IX, the competent

authority of the Member State concerned shall bring the deficiencies to the attention of the marketing authorisation holder and give the marketing authorisation holder the opportunity to submit comments.

In such case the Member State concerned shall inform the other Member States, the Agency and the Commission accordingly.

Where appropriate, the Member State concerned shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties as laid down in Article 206.

Article 189

Cooperation on inspections

1. Upon request by one or more competent authorities, inspections referred to in Article 188, paragraphs 3 and 5, may be carried out by official representatives from more than one Member State, together with the inspectors of the Agency in accordance with Article 52(2), point (a) of [revised Regulation (EC) 726/2004] ('the joint inspection').

   The competent authority of the Member State receiving a request for a joint inspection, shall make all reasonable efforts to accept such a request, and coordinate and support that joint inspection, where:

   (a) it is demonstrated, or there are reasonable ground for suspecting, that the activities carried out on the territory of the Member State receiving the request pose a risk to the safety and quality in the Member State of the competent authority requesting the joint inspection;

   (b) competent authorities of the Member State requesting the joint inspection require specialist technical expertise available in the Member State receiving the joint inspection request;

   (c) the competent authority of the Member State receiving the request agrees that there are other reasonable grounds such as training of inspectors, sharing of good practice, for for conducting a joint inspection.

2. The competent authorities participating in a joint inspection shall conclude an agreement prior to the inspection that defines at least the following:

   (a) the scope and objective of the joint inspection;

   (b) the roles of the participating inspectors during and following the inspection, including the designation of an authority leading the inspection;

   (c) the powers and responsibilities of each of the competent authorities.

3. The competent authorities participating in the joint inspection shall commit themselves in that agreement to jointly accept the results of the inspection.

4. Where the joint inspection is conducted in one of the Member States, the competent authority leading the joint inspection shall ensure that the joint inspection is carried out in

accordance with the national legislation of the Member State in which the joint inspection takes place.

5. Member States may set up joint inspection programmes to facilitate routine joint inspections. Member States may operate such programmes under a agreement as referred to in paragraphs 2 and 3.

6. A competent authority of a Member State may request another competent authority to take over one of its inspections referred to in Article 188, paragraphs 3 and 5.

7. The other competent authority of the Member State shall communicate to the requesting competent authority whether it accepts the request to conduct the inspection within 10 days. Where it accepts, it shall be responsible as the competent authority to carry out the inspections pursuant to this Section.

8. For the purposes of paragraph 6, and when the request is agreed, the requesting competent authority shall, in a timely manner, submit the relevant information necessary to conduct the inspection to the competent authority of the Member State that accepted the request.

Article 190

Inspection guidelines

1. The Commission may adopt implementing acts to lay down the principles applicable to:

   (a) the system of supervision referred to in Article 188(1);

   (b) the joint inspections referred to in Article 189(1);

   (c) the exchange of information and cooperation in the coordination of inspections in the system of supervision between the Member States and the Agency; and

   (d) trusted non-Union regulatory authorities.

   The implementing acts referred to in the first subparagraph shall be adopted in accordance with the procedure referred to in Article 214(2).

2. Member States shall, in cooperation with the Agency, establish the form and content of the manufacturing authorisation referred to in Article 142(1) and of the wholesale distribution authorisation referred to in Article 163(1), of the report referred to in Article 188, of the certificates of good manufacturing practice and of the certificates of good distribution practices referred to in Article 188(13).

SECTION 2

CONTROLS

Article 191

Controls on medicinal products

Member States shall take all appropriate measures to ensure that the marketing authorisation holder for a medicinal product and, where appropriate, the manufacturing authorisation holder, furnish proof of the controls carried out on the medicinal product or the ingredients and of the controls carried out at an intermediate stage of the manufacturing process, in accordance with the methods laid down in Annex I.

Article 192

Submission of control reports for immunological medicinal products

For the purpose of implementing Article 191, Member States may require manufacturers of immunological products to submit to a competent authority of the Member States copies of all the control reports signed by the qualified person in accordance with Article 153.

Article 193

Batch control of specific medicinal product by Member States

1. Where it considers it necessary in the interests of public health, a Member State may require the marketing authorisation holder of:

   (a) live vaccines,

   (b) immunological medicinal products used in the primary immunisation of infants or of other groups at risk,

   (c) immunological medicinal products used in public health immunisation programmes,

   (d) new immunological medicinal products or immunological medicinal products manufactured using new or altered kinds of technology or new for a particular manufacturer, during a transitional period normally specified in the marketing authorisation,

   to submit samples from each batch of the bulk or the medicinal product for examination by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose before release on to the market unless the competent authority of another Member State has previously examined the batch in question and declared it to be in conformity with the approved specifications. In such a case the declaration of conformity issued by another Member States shall be directly recognised. Member States

shall ensure that any such examination is completed within 30 days of the receipt of the samples.

2. Where, in the interests of public health, the laws of a Member State so provide, the competent authorities of the Member State may require the marketing authorisation holder for medicinal products derived from human blood or human plasma to submit samples from each batch of the bulk or the medicinal product for testing by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose before being released into free circulation, unless the competent authorities of another Member State have previously examined the batch in question and declared it to be in conformity with the approved specifications. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples.

Article 194

Processes for the preparation of medicinal products derived from human blood or human plasma

1. Member States shall take all necessary measures to ensure that the manufacturing and purifying processes used in the preparation of medicinal products derived from human blood or human plasma are properly validated, attain batch-to-batch consistency and guarantee, insofar as the state of technology permits, the absence of specific viral contamination.

2. To this end manufacturers shall notify the competent authorities of the Member States of the method used to reduce or eliminate pathogenic viruses liable to be transmitted by medicinal products derived from human blood or human plasma. The competent authority of the Member State may submit samples of the bulk or the medicinal product for testing by a State laboratory or a laboratory designated for that purpose, either during the examination of the application pursuant to Article 29, or after a marketing authorisation has been granted.

Chapter XV
Restrictions of marketing authorisations

Article 195

Suspending, revoking or varying the terms of marketing authorisations

1. The competent authorities of the Member States or, in the case of centralised marketing authorisation, the Commission shall suspend, revoke or vary a marketing authorisation if the view is taken that the medicinal product is harmful or that it lacks therapeutic efficacy, or that the benefit-risk balance is not favourable, or that its qualitative and quantitative composition is not as declared. Therapeutic efficacy shall be considered to be lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.

2. The competent authorities of the Member States or, in the case of centralised marketing authorisation, the Commission may suspend, revoke or vary a marketing authorisation if a serious risk to the environment or public health has been identified and not sufficiently addressed by the marketing authorisation holder.

3. A marketing authorisation may also be suspended, revoked or varied where the particulars supporting the application as provided for in Articles 6, 9 to 14 or Annexes I to V are incorrect or have not been amended in accordance with Article 90, or where any conditions referred to in Articles 44, 45 and 87 have not been fulfilled or where the controls referred to in Article 191 have not been carried out.

4. Paragraph 2 also applies in cases where the manufacture of the medicinal product is not carried out in compliance with the particulars provided pursuant to Annex I, or where controls are not carried out in compliance with the control methods described pursuant to Annex I.

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

Article 196

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

1. Without prejudice to the measures provided for in Article 195, the competent authorities of the Member States and, in the case of centralised marketing authorisation, the Commission shall take all appropriate steps to ensure that the supply of the medicinal product is prohibited and the medicinal product withdrawn from the market, if the view is taken that:

   (a) the medicinal product is harmful;

   (b) it lacks therapeutic efficacy;

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

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

   (e) the controls on the medicinal product or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled; or

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

2. The competent authority of the Member State or, in the case of centralised marketing authorisation, the Commission may limit the prohibition to supply the product, or its withdrawal from the market, to those batches that are the subject of dispute.

3. The competent authority of the Member State or, in the case of centralised marketing authorisation, the Commission may, for a medicinal product for which the supply has been prohibited or that has been withdrawn from the market in accordance with paragraphs 1 and 2, in exceptional circumstances during a transitional period allow the supply of the medicinal product to patients who are already being treated with the medicinal product.

Article 197

Suspected falsified medicinal products and medicinal products with suspected quality defects

1. Member States shall have a system in place that aims at preventing medicinal products that are suspected to present a danger to health from reaching the patient.

2. The system referred to in paragraph 1 shall cover the receipt and handling of notifications of suspected falsified medicinal products as well as of medicinal products with suspected quality defects. The system shall also cover recalls of medicinal products by marketing authorisation holders or withdrawals of medicinal products from the market ordered by competent authorities of the Member States or, in the case of centralised marketing authorisation, the Commission from all relevant actors in the supply chain both during and outside normal working hours. The system shall also make it possible to recall, where necessary with the assistance of health professionals, medicinal products from patients who received such products.

3. If the medicinal product in question is suspected of presenting a serious risk to public health, the competent authority of the Member State in which that product was first identified shall, without undue delay, transmit a rapid alert notification to all Member States and all actors in the supply chain in that Member State. In the event of such medicinal products being deemed to have reached patients, urgent public announcements shall be issued within 24 hours in order to recall those medicinal products from the patients. Those announcements shall contain sufficient information on the suspected quality defect or falsification and the risks involved.

Article 198

Suspending or revoking manufacturing authorisation

In addition to the measures specified in Article 196, the competent authority of the Member State may suspend manufacture or imports of medicinal products coming from third countries, or suspend or revoke the manufacturing authorisation for a category of preparations or all preparations where Articles 144, 147, 153 and 191 are not complied with.

Article 199

Refusal, suspension or revocation within the limits of the Directive

1. An authorisation to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in this Directive.

2. No decision concerning suspension of manufacture or of importation of medicinal products coming from third countries, prohibition of supply or withdrawal from the market of a medicinal product may be taken except on the grounds set out in Articles 195(5) and 196.

Chapter XVI
General provisions

Article 200

Competent authorities of the Member States

1. Member States shall designate the competent authorities to carry out tasks under this Directive.

2. Member States shall ensure that adequate financial resources are available to provide the staff and other resources necessary for the competent authorities to carry out the activities required by this Directive and [revised Regulation (EC) No 726/2004].

3. The competent authorities of the Member States shall cooperate with each other and with the Agency and the Commission in the performance of their tasks under this Directive and [revised Regulation (EC) No 726/2004] to ensure proper application and due enforcement. The competent authorities of the Member States shall transmit to each other all necessary information.

4. The competent authority of the Member State may process personal health data from sources other than clinical studies to support their public health tasks and, in particular, the evaluation and monitoring to medicinal products, for the purpose of improving the robustness of the scientific assessment or verifying claims of the applicant or marketing authorisation holder.

   Processing of personal data under this Directive shall be subject to Regulations (EU) 2016/679 and (EU) 2018/1725, as applicable.

Article 201

Cooperation with other authorities

1. Member States, in applying this Directive, shall ensure that when questions arise with regard to the regulatory status of a medicinal product, in relation to their link to substances of human origin as referred to in Regulation (EU) No [SoHO Regulation], the competent authorities of the Member States shall consult the relevant authorities established under that Regulation.

2. Member States, in applying this Directive, shall take the necessary measures to ensure cooperation between competent authorities for medicinal products and customs authorities.

Article 202

Member States exchange of information of manufacturing or wholesale distribution authorisations of medicinal products

1. Member States shall take all appropriate measures to ensure that the competent authorities of the Member States concerned communicate to each other such information as is appropriate to guarantee that the requirements placed on the authorisations referred to in Articles 142 and 163, on the certificates referred to in Article 188(13) or on the marketing authorisations are fulfilled.

2. Upon reasoned request, Member States shall send electronically the report referred to in with Article 188 to the competent authorities of another Member State or to the Agency.

3. The conclusions reached in accordance with Articles 188(13) or 188(14) shall be valid throughout the Union.

4. However, in exceptional cases, if a Member State is unable, for reasons relating to public health, to accept the conclusions reached following an inspection under Article 188(1), that Member State shall without undue delay inform the Commission and the Agency. The Agency shall inform the Member States concerned.

5. When the Commission is informed of these divergences of opinion, it may, after consulting the Member States concerned, ask the inspector who performed the original inspection to perform a new inspection; the inspector may be accompanied by two other inspectors from Member States that are not parties to the disagreement.

Article 203

Information on prohibition of supply or other action on a marketing authorisation

1. Each Member State shall take all the appropriate measures to ensure that decisions granting marketing authorisation, refusing or revoking a marketing authorisation, cancelling a decision refusing or revoking a marketing authorisation, prohibiting supply, or withdrawing a product from the market, together with the reasons on which such decisions are based, are brought to the attention of the Agency without undue delay.

2. In addition to the notification made pursuant to Article 116 of [revised Regulation (EC) No 726/2004], the marketing authorisation holder shall declare without undue delay if such notified action is based on any of the grounds set out in Articles 195 or 196(1).

3. The marketing authorisation holder shall also make the notification pursuant to paragraph 2 in cases where the action is taken in a third country and where such action is based on any of the grounds set out Articles 195 or 196(1).

4. The marketing authorisation holder shall furthermore notify the Agency where the action referred to in paragraphs 2 or 3 is based on any of the grounds referred to in Articles 195 or 196(1).

5. The Agency shall forward notifications received in accordance with paragraph 4 to all Member States without undue delay.

6. Member States shall ensure that appropriate information about action taken pursuant to paragraphs 1 and 2 that may affect the protection of public health in third countries is without undue delay brought to the attention of the World Health Organization, with a copy to the Agency.

7. Each year, the Agency shall make public a list of the medicinal products for which marketing authorisations have been refused, revoked or suspended in the Union, whose supply has been prohibited or that have been withdrawn from the market, including the reasons for such action.

Article 204

Notification of decisions related to marketing authorisations

1. Every decision referred to in this Directive that is taken by the competent authority of a Member State shall state in detail the reasons on which it is based.

2. Such decision shall be notified to the party concerned, together with information as to the redress available to them under the laws in force and of the time limit allowed for access to such redress.

3. Decisions to grant or revoke a marketing authorisation shall be made publicly available.

Article 205

Authorisation of a medicinal product on public health grounds

1. In the absence of a marketing authorisation or of a pending application for a medicinal product authorised in another Member State in accordance with Chapter III, a Member State may for justified public health reasons authorise the placing on the market of the said medicinal product.

2. When a Member State avails itself of this possibility, it shall adopt the necessary measures in order to ensure that the requirements of this Directive are complied with, in particular those referred to in Chapters IV, VI, IX, XIII and XIV, and Article 206. Member States may decide that Article 74, paragraphs 1 to 3, shall not apply to medicinal products authorised under paragraph 1.

3. Before granting such a marketing authorisation, a Member State:

   (a) shall notify the marketing authorisation holder, in the Member State in which the medicinal product concerned is authorised, of the proposal to grant a marketing authorisation under this Article in respect of the medicinal product concerned;

   (b) may request the competent authority in that Member State to submit copies of the assessment report referred to in Article 43(5) and of the marketing authorisation in force in respect of the medicinal product concerned. If so requested, the competent authority in that Member State shall supply, within 30 days of receipt of the request, a copy of the assessment report and the marketing authorisation in respect of the medicinal product concerned.

4. The Commission shall set up a publicly available register of medicinal products authorised under paragraph 1. Member States shall notify the Commission if any medicinal product is authorised, or ceases to be authorised, under paragraph 1, including the name or corporate name and permanent address of the marketing authorisation holder. The Commission shall

amend the register of medicinal products accordingly and make this register available on their website.

Article 206

Penalties

1. Member States shall lay down the rules on penalties applicable to infringements of national provisions adopted pursuant to this Directive and shall take all measures necessary to ensure that they are implemented. The penalties must be effective, proportionate and dissuasive. Member States shall, without delay, notify the Commission of those rules and of those measures and shall notify without delay of any subsequent amendment affecting them.

   Those penalties shall not be inferior to those applicable to infringements of national law of similar nature and importance.

2. The rules referred to in paragraph 1, first subparagraph, shall address, inter alia, the following:

   (a) the manufacturing, distribution, brokering, import and export of falsified medicinal products, as well as sale at distance of falsified medicinal products to the public;

   (b) non-compliance with the provisions laid down in this Directive on manufacturing, distribution, import and export of active substances;

   (c) non-compliance with the provisions laid down in this Directive on the use of excipients;

   (d) non-compliance with the provisions laid down in this Directive on pharmacovigilance;

   (e) non-compliance with the provisions laid down in this Directive on advertising.

3. Where relevant, the penalties shall take into account the risk to public health presented by the falsification of medicinal products.

Article 207

Collection of unused or expired medicinal products

Member States shall ensure that appropriate collection systems are in place for medicinal products that are unused or have expired.

Article 208

Declaration of interests

1. In order to guarantee independence and transparency, the Member States shall ensure that members of staff of the competent authority responsible for granting authorisations,

rapporteurs and experts concerned with the authorisation and surveillance of medicinal products have no financial or other interests in the pharmaceutical industry that could affect their impartiality. These persons shall make an annual declaration of their financial interests.

2. In addition, the Member States shall ensure that the competent authority makes publicly available its rules of procedure and those of its committees, agendas for its meetings and records of its meetings, accompanied by decisions taken, details of votes and explanations of votes, including minority opinions.

Chapter XVII
Specific provisions concerning Cyprus, Ireland, Malta and the United Kingdom in respect of Northern Ireland

Article 209

Provisions relevant to the United Kingdom in respect of Northern Ireland

1. By way of derogation from Article 5, the competent authorities of the United Kingdom in respect of Northern Ireland may temporarily authorise the supply to patients in Northern Ireland of a medicinal product belonging to the categories referred to in Article 3, paragraphs 1 and 2 of [revised Regulation (EC) No 726/2004] provided that all of the following conditions are fulfilled:

   (a) the medicinal product concerned has been granted a marketing authorisation by the competent authority of the United Kingdom for parts of the United Kingdom other than Northern Ireland;

   (b) the medicinal product concerned is only made available to patients or end-consumers in the territory of Northern Ireland and is not made available in any Member State.

   The maximum validity of the temporary authorisation shall be six months.

   Notwithstanding the specified validity, the temporary authorisation shall cease to be valid if the medicinal product concerned has been granted a marketing authorisation in accordance with Article 13 of [revised Regulation (EC) No 726/2004], or if such marketing authorisation has been refused in accordance with that Article.

2. By way of derogation from Article 56(4), marketing authorisations may be granted by the competent authorities of the United Kingdom in respect of Northern Ireland:

   (a) to applicants established in parts of the United Kingdom other than Northern Ireland;

   (b) to marketing authorisation holders established in parts of the United Kingdom other than Northern Ireland, in accordance with the mutual recognition or the decentralised procedure laid down in Chapter III, Sections 3 and 4.

   The competent authorities of the United Kingdom in respect of Northern Ireland may extend marketing authorisations already granted prior to 20 April 2022 to marketing

authorisation holders established in parts of the United Kingdom other than Northern Ireland.

3. By way of derogation from Article 33, paragraphs 1, 3 and 4 and Article 35(1), if an application for marketing authorisation is submitted in one or more Member States and in the United Kingdom in respect of Northern Ireland, or if an application for marketing authorisation is submitted in the United Kingdom in respect of Northern Ireland for a medicinal product that is already being examined or has already been authorised in a Member State, the application regarding the United Kingdom in respect of Northern Ireland shall not have to be submitted in accordance with Chapter III, Sections 3 and 4, provided that all of the following conditions are fulfilled:

   (a) the marketing authorisation for the United Kingdom in respect of Northern Ireland is granted by the competent authority for the United Kingdom in respect of Northern Ireland in compliance with Union law, and such compliance with Union law is ensured during the period of validity of that marketing authorisation;

   (b) the medicinal products authorised by the competent authority for the United Kingdom in respect of Northern Ireland are made available to patients or end-consumers only in the territory of Northern Ireland, and they are not made available in any Member State.

4. The marketing authorisation holder of a medicinal product for which a marketing authorisation has already been granted for the United Kingdom in respect of Northern Ireland in accordance with Chapter III, Sections 3 and 4, before 20 April 2022 shall be allowed to withdraw the marketing authorisation for the United Kingdom in respect of Northern Ireland from the mutual recognition or the decentralised procedure and to submit an application for a marketing authorisation for that medicinal product to the competent authorities of the United Kingdom with respect to Northern Ireland in accordance with paragraph 1.

5. With regard to quality control testing referred to in Article 8 carried out in parts of the United Kingdom other than Northern Ireland regarding medicinal products included in the list referred to in Article 211(9) other than those authorised by the Commission, the competent authorities of the United Kingdom in respect of Northern Ireland may consider that there is a justifiable case within the meaning of Article 8, point (b), without carrying out a case-by-case assessment provided that:

   (a) each batch of the medicinal products concerned is released by a qualified person on a site in the Union or in Northern Ireland or by a qualified person on a site in parts of the United Kingdom other than Northern Ireland applying quality standards that are equivalent to those laid down in Article 153;

   (b) the establishment designated by the third party conducting the quality control testing is supervised by the competent authority of the United Kingdom, including by performing on-the-spot checks;

   (c) where the batch release is carried out by a qualified person who resides and operates in parts of the United Kingdom other than Northern Ireland, the manufacturing authorisation holder declares that it does not have at its disposal a qualified person who resides and operates in the Union on 20 April 2022.

6. By way of derogation from Article 142(1), the competent authorities of the United Kingdom in respect of Northern Ireland shall allow medicinal products to be imported from parts of the United Kingdom other than Northern Ireland by a wholesale distribution authorisation holders as referred to in Article 163(1) that are not in possession of a relevant manufacturing authorisation provided that all of the following conditions are fulfilled:

(a) the medicinal products have undergone quality control testing either in the Union, as provided for in Article 153(3), or in parts of the United Kingdom other than Northern Ireland in compliance with Article 8, point (b);

(b) the medicinal products have been subject to batch release by a qualified person in the Union in accordance with Article 153(1) or, for medicinal products authorised by the United Kingdom in respect of Northern Ireland, in parts of the United Kingdom other than Northern Ireland applying quality standards that are equivalent to those laid down in Article 153(1);

(c) the marketing authorisation for the medicinal product concerned has been granted in accordance with Union law, by the competent authority of a Member State or by the Commission or, as regards medicinal products placed on the market in Northern Ireland, by the competent authority of the United Kingdom in respect of Northern Ireland;

(d) medicinal products are only made available to patients or end-consumers in the Member State into which the medicinal products are imported, or, if imported into Northern Ireland, are only made available to patients or end-consumers in Northern Ireland;

(e) the medicinal products bear the safety features referred to in Article 67.

7. For batches of medicinal products that are exported to parts of the United Kingdom other than Northern Ireland from a Member State and subsequently imported into Northern Ireland, the controls upon importation referred to in Article 153(1), first and second subparagraphs, shall not be required, provided that those batches have undergone such controls in a Member State prior to being exported to parts of the United Kingdom other than Northern Ireland and that they are accompanied by the control reports referred to in Article 153(1), third subparagraph.

8. Where the manufacturing authorisation is granted by the competent authority of the United Kingdom in respect of Northern Ireland, the qualified person referred to in Article 151(1) may reside and operate in parts of the United Kingdom other than Northern Ireland. This paragraph shall not apply where the manufacturing authorisation holder already has at its disposal a qualified person who resides and operates in the Union on 20 April 2022.

9. By way of derogation from the Article 99(5), where the marketing authorisation is granted by the competent authority of United Kingdom in respect of Northern Ireland, the qualified person referred to in Article 99(4), point (a), may reside and operate in parts of the United Kingdom other than Northern Ireland. This paragraph shall not apply where the marketing authorisation holder already has at its disposal a qualified person who resides and operates in the Union on 20 April 2022.

10. The competent authorities of the United Kingdom in respect of Northern Ireland shall publish on their website a list of medicinal products to which they have applied or intend to

apply the derogations as set out in this Article and shall ensure that the list is updated and managed in an independent manner, at least on a six-monthly basis.

Article 210

Regulatory functions carried out in the United Kingdom

1. The Commission shall continuously monitor developments in the United Kingdom that could affect the level of protection regarding the regulatory functions referred to in Article 99(4), Article 151(3), Article 211, paragraphs 1, 2, 5 and 6, Article 209, paragraphs 6 and 7, that are carried out in parts of the United Kingdom other than Northern Ireland taking into account, in particular, the following elements:

   (a) the rules governing the granting of marketing authorisations, the obligations of the marketing authorisation holder, the granting of manufacturing authorisations, the obligations of the manufacturing authorisation holder, the qualified persons and their obligations, quality control testing, batch release and pharmacovigilance as laid down in United Kingdom law;

   (b) whether the competent authorities of the United Kingdom ensure the effective enforcement within their territory of the rules referred to in point (a), by means of, inter alia, inspections and audits of marketing authorisation holders, manufacturing authorisation holders and wholesale distributors located in their territories, and on-the-spot checks at their premises regarding the exercise of the regulatory functions referred to in point (a).

2. Where the Commission finds that the level of protection of public health ensured by the United Kingdom through rules governing the production, distribution and use of medicinal products as well as the effective enforcement of those rules is no longer essentially equivalent to that guaranteed within the Union, or where sufficient information is not available to the Commission to enable it to establish whether an essentially equivalent level of protection of public health is ensured by the United Kingdom, the Commission shall inform the United Kingdom through a written notification of that finding and of the detailed reasons therefor.

   For a period of six months following the written notification made pursuant to the first subparagraph, the Commission shall enter into consultations with the United Kingdom with a view to remedying the situation giving rise to that written notification. In justified cases, the Commission may extend that period by three months.

3. If the situation giving rise to the written notification made pursuant to paragraph 2, first subparagraph, is not remedied within the time limit referred to in paragraph 2, second subparagraph, the Commission shall be empowered to adopt a delegated act amending or supplementing the provisions among those referred to in paragraph 1 whose application shall be suspended.

4. Where a delegated act pursuant to paragraph 3 has been adopted, the provisions referred to in the introductory sentence of paragraph 1 as specified in the delegated act shall cease to apply on the first day of the month following the entry into force of the delegated act.

5. Where the situation giving rise to the adoption of the delegated act pursuant to paragraph 3 has been remedied, the Commission shall adopt a delegated act specifying those suspended provisions that shall apply again. In that case, the provisions specified in the delegated act adopted pursuant to this paragraph shall apply again on the first day of the month following the entry into force of the delegated act referred to in this paragraph.

Article 211

Provisions relevant to Cyprus, Ireland and Malta and applicable until 31 December 2024

1. By way of derogation from Article 56(4), marketing authorisations may be granted in accordance with the mutual recognition or the decentralised procedure laid down in Chapter III, Sections 3 and 4, to marketing authorisation holders established in parts of the United Kingdom other than Northern Ireland.

   Until 31 December 2024, the competent authorities of Cyprus, Ireland and Malta marketing authorisations already granted prior to 20 April 2022 may be extended to marketing authorisation holders established in parts of the United Kingdom other than Northern Ireland.

   The marketing authorisations granted or extended by the competent authorities of Cyprus, Ireland or Malta in accordance with the first and second subparagraphs shall cease to be valid at the latest on 31 December 2026.

2. With regard to quality control testing referred to in Article 8 carried out in parts of the United Kingdom other than Northern Ireland regarding medicinal products included in the list referred to in paragraph 9, other than those authorised by the Commission, and, until 31 December 2024, the competent authorities of Cyprus, Ireland and Malta may consider that there is a justifiable case within the meaning of Article 8, point (b), without carrying out a case-by-case assessment provided that:

   (a) each batch of the medicinal products concerned is released by a qualified person on a site in the Union or in Northern Ireland or by a qualified person on a site in parts of the United Kingdom other than Northern Ireland applying quality standards that are equivalent to those laid down in Article 153(1);

   (b) the establishment designated by the third party conducting the quality control testing is supervised by the competent authority of the United Kingdom, including by performing on-the-spot checks;

   (c) where the batch release is carried out by a qualified person who resides and operates in parts of the United Kingdom other than Northern Ireland, the manufacturing authorisation holder declares that it does not have at its disposal a qualified person who resides and operates in the Union on 20 April 2022.

3. By way of derogation from Article 142(1), the competent authorities of Cyprus, Ireland and Malta shall allow medicinal products to be imported from parts of the United Kingdom other than Northern Ireland by wholesale distribution authorisation holders as referred to in Article 163(1) that are not in possession of a relevant manufacturing authorisation provided that all of the following conditions are fulfilled:

(a) the medicinal products have undergone quality control testing either in the Union, as provided for in Article 153(3), or in parts of the United Kingdom other than Northern Ireland in compliance with Article 8, point (b);

(b) the medicinal products have been subject to batch release by a qualified person in the Union in accordance with Article 153(1) or, for medicinal products authorised by the competent authorities the United Kingdom in respect of Northern Ireland, in parts of the United Kingdom other than Northern Ireland applying quality standards that are equivalent to those laid down in Article 153(1);

(c) the marketing authorisation for the medicinal product concerned has been granted in accordance with Union law, by the competent authority of a Member State or by the Commission or, as regards medicinal products placed on the market in Northern Ireland, by the competent authority of the United Kingdom in respect of Northern Ireland;

(d) medicinal products are only made available to patients or end-consumers in the Member State into which the medicinal products are imported, or, if imported into Northern Ireland, are only made available to patients or end-consumers in Northern Ireland;

(e) the medicinal products bear the safety features referred to in Article 67.

Article 166(1), point (b), shall not apply to imports that fulfil the conditions laid down in the first subparagraph.

4. For batches of medicinal products that are exported to parts of the United Kingdom other than Northern Ireland from a Member State and subsequently imported until 31 December 2024 into Cyprus, Ireland or Malta, the controls upon importation referred to Article 153(1), first and second subparagraphs, shall not be required, provided that those batches have undergone such controls in a Member State prior to being exported to parts of the United Kingdom other than Northern Ireland and that they are accompanied by the control reports referred to in Article 153(1), third subparagraph.

5. By way of derogation from Article 205(1) until 31 December 2024, in the absence of a marketing authorisation or of a pending application for a marketing authorisation the competent authorities of Cyprus and Malta may authorise for justified public health reasons the placing on their national market of a medicinal product authorised in parts of the United Kingdom other than Northern Ireland.

The competent authorities of Cyprus and Malta may also maintain in force or, until 31 December 2024, extend marketing authorisations that were granted pursuant to Article 205(1) before 20 April 2022 and that authorise the placing on their national market of a medicinal product authorised in parts of the United Kingdom other than Northern Ireland.

Authorisations that are granted, extended or maintained in force pursuant to the first or second subparagraphs shall not be valid after 31 December 2026.

6. By way of derogation from Article 56(4), the competent authorities of Malta and Cyprus may grant marketing authorisations as referred to in paragraph 5 to marketing authorisation holders established in parts of the United Kingdom other than Northern Ireland.

7. Where the competent authorities of Cyprus or Malta grant or extend a marketing authorisation as referred to in paragraph 5, they shall ensure compliance with the requirements of this Directive.

8. Before granting a marketing authorisation pursuant to paragraph 5, the competent authorities of Cyprus or Malta:

   (a) shall notify the marketing authorisation holder in parts of the United Kingdom other than Northern Ireland of the proposal to grant a marketing authorisation or to extend a marketing authorisation under paragraphs 5 to 8 in respect of the medicinal product concerned;

   (b) may request the competent authority in the United Kingdom to submit the relevant information regarding the marketing authorisation of the medicinal product concerned.

9. The competent authorities of Cyprus, Ireland, Malta shall publish on their website a list of medicinal products to which they have applied or intend to apply the derogations as set out in this Article and shall ensure that the list is updated and managed in an independent manner, at least on a six-monthly basis.

Article 212

Derogations for medicinal products placed on the markets of Cyprus, Ireland, Malta or Northern Ireland

The derogations set out in Article 211, paragraphs 1 and 6, Article 8, Article 209, paragraphs 6 and 7, Article 153 (3), Article 99(4) and Article 211(5) shall not affect the obligations of the marketing authorisation holder to ensure the quality, safety and efficacy of the medicinal product placed on the markets of Cyprus, Ireland, Malta or Northern Ireland laid down in this Directive.

Chapter XVIII
Final provisions

Article 213

Amendment to the Annexes

The Commission is empowered to adopt delegated acts in accordance with Article 215 amending Annexes I to VI in order to adapt them to scientific and technical progress and amend Article 22 with regard to the ERA requirements set out in paragraphs 2, 3, 4 and 6 of that Article.

Article 214

Standing Committee on Medicinal Products for Human Use

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use. That Committee shall be a committee within the meaning of Regulation (EU) No 182/2011.

2. Where reference is made to this paragraph, Article 5 of Regulation (EU) No 182/2011 shall apply.

3. Where the opinion of the 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 rules of procedure of the Standing Committee on Medicinal Products shall be made publicly available.

5. The Standing Committee on Medicinal Products for Human Use shall ensure that its rules of procedure are adapted to the need to make medicinal products swiftly available to patients and take account of the tasks incumbent upon it under Chapter III and the procedure set out in Article 42.

Article 215

Exercise of the delegations

1. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.

2. The power to adopt delegated acts referred to in Articles 4(2), 24(5), 25(9), 26(3), 28, paragraphs 2 and 3, 27(3), 63(5), 65(2), 67(2), 88(1), 92(4), 126(1), 150(3), 153(4), 161, 210(4) and 213 shall be conferred on the Commission for a period of five years from [OP please insert the date of the entry into force of this Directive]. The Commission shall draw up a report in respect of the delegation of power not later than nine months before the end of the five-year period. The delegation of power shall be tacitly extended for periods of an identical duration, unless the European Parliament or the Council opposes such extension not later than three months before the end of each period.

   The power to adopt delegated acts referred to in Article 210, paragraphs 3 and 5, shall be conferred on the Commission for an indeterminate period of time from [OP please insert the date = the date of the entry into force of this Directive].

3. The delegation of power referred to in Articles 4(2), 24(5), 25(9), 26(3), 27(3), 28, paragraphs 2 and 3, 63(5), 65(2), 67(2), 88(1), 92(4), 126(1), 150(3), 153(4), 161, 210(4) and 213 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 6(2), 26(3), 24(5), 28, paragraphs 2 and 3, 27(3), 63(5), 65(2), 67(2), 88(1), 92(4), 126(1), 150(3), 153(4), 161, 210(4) and 213 shall enter into force only if no objection has been expressed either by the European Parliament or by the Council within a period of two months of notification of that act to the European Parliament and the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by two months at the initiative of the European Parliament or of the Council.

Article 216

Report

By [OP please insert the date = 10 years following 18 months after the date of entering into force of this Directive], the Commission shall present a report to the European Parliament and the Council on the application of this Directive, including an assessment of the fulfilment of its objectives and the resources required to implement it.

Article 217

Repeals

1. Directive 2001/83/EC is repealed with effect from [OP please insert the date = 18 months after the date of entering into force of this Directive].

2. Directive 2009/35/EC is repealed with effect from [OP please insert the date = 18 months after the date of entering into force of this Directive].

3. References to the repealed Directives 2001/83/EC and 2009/35/EC shall be construed as references to this Directive. References to the repealed Directive 2001/83/EC shall be read in accordance with the correlation table in Annex VIII.

Article 218

Transitional provisions

1. The procedures concerning the applications for marketing authorisations for medicinal products validated in accordance with Article 19 of Directive 2001/83/EC before [OP please insert the date = 18 months after the date of entering into force of this Directive] and that were pending on [OP please insert the date = the day before 18 months after the date of entering into force of this Directive] shall be completed in accordance with Article 29.

2. Procedures initiated on the basis of Articles 29, 30, 31, and 107i of Directive 2001/83/EC before [OP please insert the date = 18 months after the date of entering into force of this Directive] and that were pending on [OP please insert the date = the day before 18 months after the date of entering into force of this Directive] shall be completed in accordance with Articles 32 to 34 or Article 107k, as appropriate, of that Directive as applicable on [OP

please insert the date = the day before 18 months after the date of entering into force of this Directive].

3. This Directive shall also apply to medicinal products authorised in accordance with Directive 2001/83/EC before [OP please insert the date = 18 months after the date of entering into force of this Directive].

   This Directive shall also apply to registrations of homeopathic medicinal products and traditional herbal medicinal products carried out in accordance with Directive 2001/83/EC before [OP please insert the date = 18 months after the date of entering into force of this Directive].

4. By way of derogation from Chapter VI, the medicinal products placed on the market in accordance with Directive 2001/83/EC before [OP please insert the date = 18 months after the date of entering into force of this Directive] may continue to be made available on the market until [OP please insert the date = five years after 18 months after the date of entering into force of this Directive], provided that they comply with the provision on labelling and package leaflet set out in Title V of Directive 2001/83/EC as applicable on [OP please insert the date = the day before 18 months after the date of entering into force of this Directive].

5. By way of derogation from Article 81, reference medicinal products for which the application for marketing authorisation has been submitted before [OP please insert the date = 18 months after the date of entering into force of this Directive] shall be subject to the provisions on data protection periods set out in Article 10 of Directive 2001/83/EC as applicable on [OP please insert the date = 18 months after the date of entering into force of this Directive] until [OP please insert the date = 18 months after the date of entering into force of this Directive].

6. By way of derogation from paragraph 3, the reporting obligations as referred to in Article 57, shall not apply with regards to medicinal products authorised in accordance with Directive 2001/83/EC before [OP please insert the date = 18 months after the date of entering into force of this Directive].

Article 219

Transposition

1. Member States shall bring into force the laws, regulations and administrative provisions to comply with this Directive by [18 months after the date of entering into force of this Directive]. They shall immediately communicate the text of those measures to the Commission.

2. When Member States adopt those measures, they shall contain a reference to this Directive or be accompanied by such reference on the occasion of their official publication. They shall also include a statement that references in existing laws, regulations and administrative provisions to the Directives repealed by this Directive shall be construed as references to this Directive. Member States shall determine how such reference is to be made and how that statement is to be formulated.

3. Member States shall communicate to the Commission the text of the main measures of national law that they adopt in the field covered by this Directive.

Article 220

Entry into force

This Directive shall enter into force on the twentieth day following that of its publication in the *Official Journal of the European Union*.

Article 221

Addressees

This Directive is addressed to the Member States.

Done at Brussels,

For the European Parliament	*For the Council*
The President	*The President*