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COMMISSION OF THE EUROPEAN COMMUNITIES

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Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

**amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code
relating to medicinal products for human use**

{SEC(2008) 2670}
{SEC(2008) 2671}

EXPLANATORY MEMORANDUM

1. CONTEXT OF THE PROPOSAL

1.1. Grounds for and objectives of the proposal

Medicinal products contribute considerably to the health of EU citizens. The discovery, development and effective use of medicinal products improve quality of life, reduce the length of time spent in hospital and save lives. Medicinal products can, however, also have adverse effects and adverse drug reactions present an important public health burden in the Community. It is estimated that 5% of all hospital admissions are due to an adverse drug reaction, 5% of all hospital patients suffer an adverse drug reaction and adverse drug reactions are the fifth most common cause of hospital death.

Some adverse reactions will only be detected after a medicine has been authorised and the full safety profile of medicinal products can only be known once they have entered the market. Pharmacovigilance rules are therefore necessary for the protection of public health in order to prevent, detect and assess adverse effects of medicinal products.

Community rules so far adopted have made a major contribution to the achievement of the objective that medicinal products authorised to be placed on the Community market are continuously monitored as regards their safety. However, in the light of the experience acquired and following an assessment by the Commission of the Community system of pharmacovigilance, it has become clear that new measures are necessary to improve the operation of the Community rules on the pharmacovigilance of medicinal products for human use.

Therefore, the proposals aim at the strengthening and rationalizing the Community pharmacovigilance system of medicinal products for human use through the amendment of the two legal acts governing this field, with the overall objectives of better protecting public health, ensuring proper functioning of the internal market. and simplifying the current rules and procedures. The specific objectives are:

- Providing for clear roles and responsibilities for the key responsible parties and clear obligations against which they perform their roles;
- Rationalising EU decision-making on drug safety issues in order to deliver measures that are equally and fully implemented for all relevant products and across the Community with a view to preventing unnecessary patient exposure to risks;
- Strengthening medicines safety transparency and communication to increase the understanding and trust of patients and health professionals in the safety of medicines and improve the penetration of key warnings;
- Strengthening companies' pharmacovigilance systems, allowing companies to improve their systems constantly while reducing administrative burden;
- Ensuring the proactive and proportionate collection of high quality data relevant to the safety of medicines through risk management and structured data collection

in the form of post authorisation safety studies, together with rationalised single case and periodic reporting of suspected adverse reactions;

- Involving stakeholders in pharmacovigilance including through direct patient reporting of suspected adverse reactions and inclusion of patients and health-care professionals in decision-making.
- Simplification of the current Community pharmacovigilance procedures with consequent efficiency gains for both the pharmaceutical industry and medicines regulators.

1.2. General context

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects of medicinal products.

The Community has had legislation on medicinal products on pharmacovigilance since 1965. Until now there has been no systematic review of the Community pharmacovigilance legislation, its operation and its effect on protecting public health. Therefore, in 2004 the Commission services launched an independent study into the functioning of the Community pharmacovigilance system. The independent report together with a subsequent broad public consultation revealed several shortcomings.

1.3. Existing provisions in the area of the proposal

Harmonised Community rules on the pharmacovigilance of medicinal products for human use are laid down in:

- 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 Agency¹, as regards medicinal products authorized by the Commission in accordance with the procedure of that Regulation (the so-called "centralised procedure"); and
- 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 use², as regards general rules on medicinal products for human use and specific rules for medicinal products authorised by the Member States.

While the rules are broadly the same in substance, there are certain divergences and various provisions are duplicated in the two legal texts. It is appropriate to rationalise and simplify this by laying down all general rules in the Community code on medicinal products for human use (Directive 2001/83/EC), and cross-referring to them in the regulation governing the centralised procedure (Regulation (EC) No 726/2004), with specific provisions for centrally authorised products only when justified.

¹ OJ L 136, 30.4.2004, p. 1.

² OJ L 311, 28.11.2001, p. 67.

1.4. Consistency with the other policies and objectives of the Union

The proposals are consistent with the overall objective of the Community legislation on medicinal products for human use, which is to remove disparities between national provisions in order to ensure the proper functioning of the internal market for such products, while at the same time safeguarding a high level of protection of public and human health. They are also consistent with Article 152(1) of the Treaty establishing the European Community, which provides that a high level of human health protection shall be ensured in the definition and implementation of all Community policies and activities.

The proposal is equally consistent with the Commission patient safety initiative³ and the Commission work to stimulate innovation in the pharmaceutical sector, through the 7th Framework programme in general and the Innovative Medicines Initiative⁴ in particular. The proposal is also consistent with Community projects which aim to develop and validate the use of innovative information technology tools to identify medicines adverse events⁵.

2. CONSULTATION OF INTERESTED PARTIES AND IMPACT ASSESSMENT

2.1. Consultation of interested parties

All interested parties, in particular patient and healthcare professionals, Member States competent authorities and industry, have been widely consulted on this proposal. Various means of consultation have been used, namely two internet-based public consultations, dedicated workshops, questionnaires and bilateral meetings.

Additional information on the consultations conducted can be found in the Impact Assessment attached to this proposal. The detailed results of both parts of the consultation, including the individual consultation responses can be found at:

http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance/pharmacovigilance_key.htm

2.2. Impact assessment

The details of the impact assessment are provided in the Commission Staff Working Document 'Impact Assessment' attached to this proposal.

In conclusion, the impact assessment suggests that increasing the clarity, efficiency and quality of the EU system of pharmacovigilance, through amendments to the existing Community legal framework, leads to major public health improvements and overall cost savings to the EU industry sector.

³ See: http://ec.europa.eu/health/ph_overview/patient_safety/consultation_en.htm

⁴ See: http://imi.europa.eu/documents_en.html

⁵ A number of Community projects aim at providing insights to improve pharmacovigilance by analysing, using information technology, the information available in Electronic Health Records, including projects co-funded under the 7th Framework Research Programme.

3. LEGAL ELEMENTS OF THE PROPOSAL

3.1. Summary of the proposed action

The key elements of the proposals can be summarised as follows:

Clear roles and responsibilities

Current legislation contains some instances of overlapping or ambiguous responsibilities for pharmacovigilance.

The **tasks and responsibilities of involved parties in the legislation** (Member State, Agency, marketing authorisation holders) are clarified and codified and the concept and scope of Good Vigilance Practices for all involved in pharmacovigilance is established. The key tasks of the Agency in the area of pharmacovigilance laid down in Regulation (EC) No 726/2004 are overall maintained, but the Agency's coordinating role at the centre of the Community pharmacovigilance system is reinforced. The Member States should remain core to the operation of pharmacovigilance in the Community, with increased cooperation and work-sharing mechanisms. The pharmacovigilance responsibilities of marketing authorisation holders are also clarified, in particular as regards the scope of the obligation of marketing authorisation holders to continuously monitor the safety of products to ensure that all information available is brought to the attention of the authorities.

A **new scientific committee responsible for pharmacovigilance** is created within the Agency, the Pharmacovigilance Risk Assessment Advisory Committee. The Committee is intended to play a key role in the pharmacovigilance assessments in the Community, by providing support both to the Committee for Medicinal Products for Human Use within the Agency (responsible for opinions on the quality, safety and efficacy of medicinal products for human use in the framework of Community procedures), and the coordination group of Member States established by Directive 2001/83/EC (involved in the national authorisation procedures).

The **mandate of the coordination group** composed of Member States representatives set up by Article 27 of Directive 2001/83/EC is enhanced for the sake of closer cooperation between the Member States in the area of pharmacovigilance and in order to increase work-sharing.

The **Community procedure for the assessment of serious safety issues for nationally authorised products** is stream-lined through clear and binding initiation criteria for the Member States, rules to ensure that all products concerned are considered, an assessment procedure by the Pharmacovigilance Risk Assessment Advisory Committee, and rules for the subsequent follow-up as regards the terms of the marketing authorisations with a view to the adoption of harmonised measures across the Community.

Transparency and communication

Strengthened medicines safety transparency and communication should increase the understanding and trust of patients and health professionals in the safety of medicines and the regulatory system. Clear, EU coordinated messages about specific safety risk issues will improve the safe use of medicines.

Strengthening of the Eudravigilance database which should become the single point of receipt of pharmacovigilance information for medicinal products for human use authorised in the Community, therefore allowing all competent authorities to receive, access and share the information at the same time, with appropriate access to the Eudravigilance database data ensured.

Community coordination of communication about safety issues and establishment of a European medicines safety web-portal: The principles of communications about major new or changing safety issues should be laid down in the legislation. For issues affecting active substances authorised in more than one Member State, the Agency should coordinate the communications of the Member States. Furthermore, the Agency should set-up and maintain an European medicines safety web-portal as the main platform for announcements related to medicines safety dealt with at the EU level, and would include links to web-portals of the Member State competent authorities.

Introduction of a **new 'key information' section in the summary of the product characteristics and the package leaflet** which accompany every medicinal product placed on the Community market.

Pharmacovigilance obligations by the marketing authorisation holder

Currently legislation requires a 'detailed description of the pharmacovigilance system' to be submitted in marketing authorisation applications and kept up to date for each individual marketing authorisation. The proposals simplify the existing requirement.

"Pharmacovigilance system master file": In the marketing authorisation application only key elements of the pharmacovigilance system should be submitted, but this is balanced with a requirement for companies to maintain a detailed file on site.

Risk management planning and non-interventional safety studies

Rationalising of risk management planning should ensure that safety evaluation of products is prospective (i.e. based on risk management planning) and that high-quality, non-promotional safety studies are done when justified by safety concerns.

In the provisions currently in force, applicants for a marketing authorisation may provide a **risk management system for specific medicinal** products if considered appropriate, and there is no explicit legal basis for competent authorities to request it. The proposals require a risk management system for each medicinal product to be newly authorised in the Community (or for existing products on the basis of safety concerns), which should be proportionate to the identified risks, potential risks, and the need for additional information on the medicinal product.

Harmonised guiding principles and a procedure for the supervision of non-interventional post-authorisation safety studies (i.e. safety studies of authorised products that are not clinical trials), in particular to ensure that they are non promotional, and the follow-up of any safety data generated in such studies.

Adverse drug reaction case reports

Current reporting rules apply equally to all medicinal products, irrespective of their known risks, are submitted to several authorities where a product is authorised in more than one

Member State, and lead to duplicative assessments as there is no provision to group assessments by products or substances. Besides, the notion of adverse reaction is linked to the side effects under normal conditions of use of medicinal products, and other side effects (resulting e.g. from medication errors or overdose) are not necessarily reported. The proposals are intended to make reporting proportionate to risks, to empower patients to report their side effects, and to ensure that overdoses and medication errors are reported.

Simplification of adverse reaction reporting. It is proposed to considerably simplify reporting rules by providing that all adverse reaction data are reported by marketing authorisation holders and Member States directly to the Eudravigilance database. As a result of this new reporting scheme, it will not be longer necessary to provide for different reporting rules for medicinal products authorised in accordance with the centralised procedure and medicinal products authorised in the Member States.

Monitoring of scientific literature by the Agency: The Agency is to take on a new task for the monitoring of selected scientific literature and for entering case reports of adverse effects onto the Eudravigilance database.

Medication errors that result in an adverse reaction should be reported to the competent authorities for medicines: The definition of adverse drug reaction should be clarified to make clear that companies report medication errors that result in an adverse reaction to the competent authorities for medicines and ensure that all the relevant Member State authorities share data (including between the authorities for medicines and any authorities for patient safety).

Make clear the **legal basis for patients to report** suspected adverse drug reactions.

Periodic safety update reports and other safety related assessments

Currently, periodic safety update reports are line listings of adverse reactions and, as for adverse reactions reports, are submitted for all medicinal products. Since there is no provision to group submissions and assessments by products or substances, this leads to duplicative submissions and assessments. The update of product information as a result of these assessments is not governed in detail by the actual legislation. The proposals simplify periodic safety update report submission by industry and make it proportional to the knowledge about the safety/risk of the product, would introduce work-sharing mechanisms for the assessments, with a prominent role in all cases by the Pharmacovigilance Risk Assessment Advisory Committee, and faster updating of product information through the establishment of clear procedures.

As a result of the submission of all adverse reaction data directly to the Eudravigilance database, the **scope of periodic safety update reports** is amended to become an analysis of the risk-benefit balance of a medicinal product rather than a detailed presentation of individual case reports. Besides, the **requirements for periodic safety update reports are made proportional to the risks** posed by medicinal products, and routine reporting is no longer necessary for products considered low risk or where reporting would be duplicative (with the possibility for ad-hoc requests for such products).

Explicit provision is made for the **regulatory follow-up of assessments of periodic safety update reports**, to ensure a clear link between pharmacovigilance evaluations and the review and updating of marketing authorisations authorised in the Community.

The proposals create the **framework for the shared use of resources between competent authorities for the assessment and follow-up of periodic safety update reports**, with a strong involvement of the Agency's Pharmacovigilance Risk Assessment Advisory Committee. A single assessment of periodic safety update reports for medicinal products authorised in more than one Member State, including for all products containing the same active substance, is foreseen. To further increase the efficiency of the system, a single assessment would also be conducted in the case of pharmacovigilance issues which concern products authorised by the Member States and products authorised by the Commission.

3.2. Legal basis

The proposal is based on Article 95 of the EC Treaty. Article 95, which prescribes the codecision procedure described in Article 251, is the legal basis for achieving the aims set out in Article 14 of the Treaty, which includes the free movement of goods (Article 14(2)), in this case medicinal products for human use.

While taking account of the fact that any regulation on medicinal products must be fundamentally aimed at safeguarding public health, since the Amsterdam Treaty came into force, Article 95 is the legal basis of the Community legislation for medicinal products for human use, including Directive 2001/83/EC and Regulation (EC) No 726/2004⁶, since the differences between the national legislative, regulatory and administrative provisions on medicinal products tend to hinder intra-Community trade and therefore directly affect the operation of the internal market. Action to promote the development and authorisation of medicinal products is hence justified at a European level, with a view to preventing or eliminating these obstacles.

3.3. Subsidiarity principle

Community rules in the area of pharmacovigilance allow the best protection of public health according to the same standards across the Community. Divergent action by the Member States would prevent the full sharing of safety data and would increase the administrative burden on competent authorities and industry. A lack of coordination would deny the Member States access to the best scientific and medicinal expertise for the evaluation of the safety of medicines and for risk minimisation.

The impact analysis has shown that the ongoing efforts to improve the Community pharmacovigilance system through better implementation of the current legal framework, while bringing genuine improvements to the system, would be insufficient to make the step change improvement needed to reduce the major public health burden of adverse reactions to medicinal products.

3.4. Proportionality principle

The proposal has been carefully designed in close dialogue with stakeholders particularly those stakeholders upon which direct obligations are placed by the legal provisions, in order to better protect public health without imposing an unnecessary regulatory burden. The proposal builds on existing structures (including the European Medicines Agency and Member State competent authorities), procedures (including the existing reporting and referral procedures),

⁶ Regulation (EC) No 726/2004 is also based on Article 152(4)(b), as regards the regulation of veterinary medicinal products, outside the scope of the current proposals.

resources (including the existing Community pharmacovigilance database) and practices (including work-sharing by the Member States). The proposal strives to maximise the efficiency of the processes and maximise the quality of the data collected and the quality of decisions taken thereby maximally benefiting public health. By increasing the efficiency of the Community pharmacovigilance system, the proposal will free up resource currently expended on meeting duplicative and complex administrative requirements and these resources can then be channelled into activities that directly promote and protect public health including better communications about the benefits and risks of medicines

The proposal does not go beyond what is necessary to achieve the objective pursued, i.e. to strengthen and rationalise Community pharmacovigilance system. The Impact Assessment has shown cost savings for the industry with an increase in costs for the regulators (national competent authorities and the Agency) that will be covered by industry fees. This increase in costs is modest compared to the projected savings to society including from reductions in hospitalisations and prolonged hospital stays caused by adverse reactions to medicinal products.

3.5. Choice of instruments

The proposal aims at modifying the existing provisions on pharmacovigilance for medicinal products for human use contained in Regulation (EC) No 726/2004 and in Directive 2001/83/EC, and an amending regulation and an amending directive are therefore considered the most appropriate legal instruments.

4. BUDGETARY IMPLICATION

The proposal has no implication for the Community budget.

5. ADDITIONAL INFORMATION

5.1. Simplification

This initiative is referenced in the Commission Agenda Planning as 2008/ENTR/003. It is part of the Commission Legislative and Work Programme for 2008, under Annex 1 (Strategic and Priority initiatives)⁷.

The proposals contain key elements for the simplification of the Community system of pharmacovigilance, including: closer collaboration between the authorities which will maximise the expertise available; work-sharing and a strengthened role for the coordination group of the Member States to increase the efficient use of scarce resources and reduce duplication of effort; simplified adverse reaction and periodic safety update reporting; and the Pharmacovigilance System Master File of marketing authorisation holder.

5.2. European Economic Area

The proposed act is of relevance to the EEA.

⁷ http://ec.europa.eu/atwork/programmes/docs/clwp2008_en.pdf (see page 20).

Proposal for a

DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission⁸,

Having regard to the opinion of the European Economic and Social Committee⁹,

Acting in accordance with the procedure laid down in Article 251 of the Treaty¹⁰,

Whereas:

- (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 use¹¹ lays down harmonised rules for the authorisation, supervision and pharmacovigilance of medicinal products within the Community.
- (2) Pharmacovigilance rules are necessary for the protection of public health in order to prevent, detect and assess adverse effects of medicinal products placed on the market of the Community, as the full safety profile of medicinal products can only be known once they have entered the market.
- (3) In the light of the experience acquired and following an assessment by the Commission of the Community system of pharmacovigilance, it has become clear that measures are necessary to improve the operation of the Community rules on the pharmacovigilance of medicinal products for human use.

⁸ OJ C , , p. .

⁹ OJ C , , p. .

¹⁰ OJ C , , p. .

¹¹ OJ L 311, 28.11.2001, p. 67.

- (4) While taking into account the fact that the regulation of medicinal products should be fundamentally aimed at safeguarding public health, this aim should be achieved by means that do not impede the free movement of safe medicinal products within the Community. It has emerged from the assessment of the Community system of pharmacovigilance that divergent Member State action on safety issues of medicinal products is creating barriers to the free movement of medicinal products. In order to prevent or eliminate those obstacles the existing pharmacovigilance provisions at Community level should be strengthened and rationalised.
- (5) For the sake of clarity, the definition of adverse reaction should be amended to ensure that it not only covers noxious and unintended effects derived from the authorised use of a medicinal product at the normal doses, but also medication errors and uses outside the authorised summary of the product characteristics, including the misuse and abuse of the product.
- (6) The marketing authorisation holder should establish a pharmacovigilance system to ensure the monitoring and supervision of one or more of its authorised medicinal products, recorded in a Pharmacovigilance System Master File permanently accessible for inspection. The competent authorities should undertake the supervision of those systems. A summary of the pharmacovigilance system should be therefore submitted with the marketing authorisation application and include a reference to the site where the Pharmacovigilance System Master File for the medicinal product concerned is maintained and accessible for inspection.
- (7) The planning of pharmacovigilance for each individual medicinal product by the marketing authorisation holder should take place in the context of a risk management system and should be proportionate to the identified risks, potential risks, and the need for additional information on the medicinal product. It should also be foreseen that any key measures contained in a risk management system are included in the marketing authorisation as conditions.
- (8) In order to ensure the collection of any necessary additional data about the safety of authorised medicinal products, competent authorities should be empowered to require post-authorisation safety studies at the time of the granting of the marketing authorisation or later, and this requirement should be included as a condition of the marketing authorisation.
- (9) Where a medicinal product is authorized subject to the requirement to conduct a post-authorisation safety study or where there are conditions or restrictions with regard to the safe and effective use of the medicinal product, the medicinal product should be intensively monitored on the market. Patients and healthcare professionals should be encouraged to report all suspect adverse reactions to such medicinal products, and a publicly available list of such medicinal products should be maintained up to date by the European Medicines Agency established

by 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 Agency¹² (hereinafter referred to as the 'Agency').

- (10) In order to make it possible for the healthcare professionals and patients to identify easily the most relevant information about the medicines they use, the summary of the product characteristics and the package leaflet should include a concise section on the key information about the medicinal product and information how to minimize its risks and maximize its benefits.
- (11) Experience has shown that the responsibilities of marketing authorisation holders for the pharmacovigilance of authorised products should be clarified. The marketing authorisation holder should be responsible for continuously monitoring the safety of his products, for informing the authorities of any changes that might impact on the marketing authorisation, and for ensuring that the product information is maintained up to date. As medicinal products could be used outside the terms of their marketing authorisations, these responsibilities should include providing all information available, including the results of clinical trials or other studies, as well as reporting of the use of the medicinal product, which is not in accordance with the summary of the product characteristics. Likewise it is appropriate to ensure that the renewal of marketing authorisations should consider all relevant information collected on the safety of the medicinal product.
- (12) In order to ensure close cooperation between the Member States in the area of pharmacovigilance, the mandate of the coordination group set up by Article 27 of Directive 2001/83/EC should be enlarged to include the examination of questions related to the pharmacovigilance of all medicinal products authorised by the Member States. In order to fulfil its new tasks, the coordination group should be further strengthened through the adoption of clear rules as regards the expertise required, the adoption of opinions, transparency, independence and professional secrecy of its members, and the need for cooperation between Community and national bodies.
- (13) With a view to ensuring that the same level of scientific expertise in the area of pharmacovigilance decision-making at both Community and national level, when fulfilling pharmacovigilance tasks the coordination group should be able to rely on the advice of the Pharmacovigilance Risk Assessment Advisory Committee of the Agency.
- (14) In order to avoid duplication of work, a single opinion should be adopted by the coordination group for pharmacovigilance assessments concerning products authorised in more than one Member State. The agreement within the coordination group should suffice for pharmacovigilance measures to be

¹² OJ L 136, 30.4.2004, p. 1.

implemented throughout the Community. Where no agreement is found in the coordination group, the Commission should be authorised to adopt a decision to that effect, addressed to the Member States.

- (15) A single assessment should also be conducted in the case of pharmacovigilance issues which concern products authorised by the Member States and products authorised in accordance with Regulation (EC) No 726/2004. In such cases, the Commission should adopt harmonised measures for all products concerned on the basis of a Community assessment.
- (16) Member States should operate a pharmacovigilance system to collect information useful in the surveillance of medicinal products including information on suspected adverse drug reactions, on misuse, abuse and medication errors, and ensure its quality through the follow up of suspected adverse drug reaction cases.
- (17) To further increase the coordination of resources between the Member States, Member State should be authorised to delegate certain pharmacovigilance tasks to another Member State.
- (18) In order to simplify the reporting of suspected adverse reactions the marketing authorisation holders and the Member States should report those reactions only to the Community pharmacovigilance database and data-processing network referred to in Article 57(1)(d) of Regulation (EC) No 726/2004 (hereinafter ‘the Eudravigilance database’).
- (19) In order to increase the level of transparency on the processes of pharmacovigilance, the Member States should create and maintain medicines safety web-portals. To the same end, the marketing authorisation holders should provide the authorities with prior warning about safety announcements and the authorities should provide each other with such a warning.
- (20) Community rules on pharmacovigilance should continue to rely on the crucial safety monitoring role of healthcare professionals, and should take account of the fact that patients are also well placed to report adverse reactions to medicines. It is therefore appropriate to facilitate the reporting of suspected adverse reactions to medicinal products by both healthcare professionals and patients, and to make available to them methods for such reporting.
- (21) As a result of the submission of all adverse reaction data directly to the Eudravigilance database, it is appropriate to amend the scope of periodic safety update reports so that they present an analysis of the risk-benefit balance of a medicinal product rather than a detailed listing of individual case reports already submitted to the Eudravigilance database.
- (22) Requirements for periodic safety update reports should be proportional to the risks posed by medicinal products. Periodic safety update reporting should therefore be linked to the risk management system for newly authorised medicinal products

and routine reporting should not be necessary for generic, well-established use, informed consent, homeopathic, or traditional use registered herbal medicinal products. However, in the interest of public health the authorities should require periodic safety update reports for such products when there is a need to assess their risk or review the adequacy of product information.

- (23) There is a need to increase the shared use of resources between competent authorities for the assessment of periodic safety update reports. Provision should be made for a single assessment of periodic safety update reports for medicinal products authorised in more than one Member State. Moreover, procedures should be established to set single frequency and submission dates of periodic safety update reports for all products containing the same active substance or combination thereof.
- (24) Following a single assessment of periodic safety update reports, any resulting measures as regards the maintenance, variation, suspension or revocation of the marketing authorisations concerned should be adopted through a Community procedure leading to a harmonised result.
- (25) The Member States should automatically submit certain safety issues related to medicinal products to the Agency thereby triggering a Community assessment of the issue. Therefore it is appropriate to establish rules to ensure an assessment procedure by the Pharmacovigilance Risk Assessment Advisory Committee, and rules for the subsequent follow-up as regards the terms of the marketing authorisations with a view to the adoption of harmonised measures across the Community. As this procedure is triggered on the basis of a set of binding criteria, it should take precedence over other procedures which could also be used to address safety issues, such as those referred to in Articles 31 and 36 of Directive 2001/83/EC.
- (26) It is necessary to introduce harmonised guiding principles and regulatory supervision of post-authorisation safety studies that are non-interventional, that are initiated, managed or financed by the marketing authorisation holder, that involve the collection of data from patients or healthcare professionals thus falling outside the scope of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use¹³. Supervision of such studies should be the responsibility of the national competent authority for studies to be conducted in one Member State and of the Pharmacovigilance Risk Assessment Advisory Committee for studies to be conducted in more than one Member State. Provision should also be made for the subsequent follow-up, if appropriate, as regards the terms of the marketing

¹³ OJ L 121, 1.5.2001, p. 34.

authorisations with a view to the adoption of harmonised measures across the Community.

- (27) In order to enforce the provisions related to the pharmacovigilance, the Member States should ensure that effective, proportionate and dissuasive penalties are applied to marketing authorisation holders for non-compliance with pharmacovigilance obligations.
- (28) In order to protect public health, there should be adequate funding of activities related to pharmacovigilance by the national competent authorities. It should be possible to ensure adequate funding for pharmacovigilance activities through the collection of fees. However, the management of those collected funds should be under the permanent control of the national competent authorities in order to guarantee their independence.
- (29) It should be possible for Member States to allow, under certain conditions, to deviate from certain provisions of Directive 2001/83/EC related to the requirements for labelling and packaging in order to address severe availability problems related to the potential lack of authorised products or of products placed on the market or shortages thereof.
- (30) Since the objective of this directive of improving the safety of medicines placed on the market in the Community in a harmonised way across the Member States cannot be sufficiently achieved by the Member States and can be better achieved at Community level, the Community may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty. 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 this objective.
- (31) The provisions on the surveillance of medicinal products for human use in Directive 2001/83/EC constitute specific provisions in the meaning of Article 15(2) of Regulation (EC) No 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products, and repealing Regulation (EEC) No 339/93¹⁴.
- (32) Directive 2001/83/EC should therefore be amended accordingly,

¹⁴ OJ L 218, 13.8.2008, p. 30.

HAVE ADOPTED THIS DIRECTIVE:

Article 1
Amendments to Directive 2001/83/EC

Directive 2001/83/EC is amended as follows:

1. Article 1 is amended as follows:

(a) point 11 is replaced by the following:

“(11) Adverse reaction: A response to a medicinal product which is noxious and unintended.”;

(b) point 14 is replaced by the following:

“(14) Suspected adverse reaction: An adverse reaction in respect of which a causal relationship between the event and the medicinal product cannot be excluded.”;

(c) point 15 is replaced by the following:

“(15) Post-authorisation safety study: Any study with 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.”;

(d) The following points 28b, 28c and 28d are inserted:

“(28b) Risk management system: 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 interventions.

(28c) Pharmacovigilance system: a system utilized by marketing authorisation holders and by Member States to fulfil the tasks and responsibilities listed in Title IX and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.

(28d) Pharmacovigilance system master file: A detailed description of the pharmacovigilance system utilized by the marketing authorisation holder with respect to one or more authorised medicinal products.”

2. Article 8(3) is amended as follows:

(a) point (ia) is replaced by the following:

“(ia) A summary of the applicant's pharmacovigilance system which shall include the following elements:

- proof that the applicant has the services of a qualified person responsible for pharmacovigilance;
- the Member State where the qualified person resides;
- the contact details for the qualified person;
- a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX;
- a reference to the site where the pharmacovigilance system master file for the medicinal product is maintained.”;

(b) the following point (iaa) is inserted:

“(iaa) A detailed description of the risk-management system which the applicant will introduce for the medicinal product concerned.”

(c) point (l) is replaced by the following:

“(l) Copies of the following:

- any authorisation obtained in another Member State, including a summary of the data contained in periodic safety reports and adverse reactions reports, or in a third country to place the medicinal product on the market, together with a list of those Member States in which an application for authorisation submitted in accordance with this Directive is under examination;
- copies of the summary of the product characteristics proposed by the applicant in accordance with Article 11 or approved by the competent authorities of the Member State in accordance with Article 21. Copies of the package leaflet proposed in accordance with Article 59 or approved by the competent authorities of the Member State in accordance with Article 61.
- details of any decision to refuse authorization, whether in the Community or in a third country, and the reasons for such a decision.”

(d) point (n) is deleted.

(e) the following subparagraphs are added:

“The risk management system referred to in point (iaa) of the first subparagraph shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorisation safety data.

The information referred to in point (l) of the first subparagraph shall be updated on a regular basis.”

3. Article 11 is amended as follows:

(a) the following point 3a is inserted:

“(3a) a summary of the essential information necessary to use the medicine safely and effectively;

(b) the following subparagraph is added:

“For the purposes of point (3a) of the first subparagraph, for medicinal products included on the list referred to in Article 23 of Regulation (EC) No 726/2004, the summary shall include the statement: “This medicinal product is under intensive monitoring. All suspected adverse reactions should be reported to <name and web-address of the national competent authority>.”

4. Article 16g(1) is replaced by the following:

“1. Articles 3(1) and (2), 4(4), 6(1), 12, 17(1), 19, 20, 23, 24, 25, 40 to 52, 70 to 85, 101 to 108b, 111(1) and (3), 112, 116, 117, 118, 122, 123, 125, 126, second subparagraph, and 127 of this Directive as well as Commission Directive 2003/94/EC(*) shall apply, by analogy, to traditional-use registration granted under this Chapter.

(*) OJ L 262, 14.10.2003, p. 22.”

5. Article 17 is amended as follows:

(a) In the second subparagraph of paragraph 1, the figure ‘27’ is replaced by the figure ‘28’;

(b) In paragraph 2, the figure ‘27’ is replaced by the figure ‘28’;

6. In Article 18, the figure ‘27’ is replaced by the figure ‘28’.

7. In Article 21, paragraphs 3 and 4 are replaced by the following:

“3. The national competent authorities shall make publicly available without delay the marketing authorisation together with the summary of the product

characteristics and any conditions established in accordance with Articles 21a, 22 and 22a, together with any deadlines for their fulfilment, for each medicinal product which they have authorised.

4. The national competent authorities shall draw up an assessment report and comments on the file as regards the results of the pharmaceutical and pre-clinical tests, the clinical trials and the risk management system and the pharmacovigilance system of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is of importance for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

The national competent authorities shall make publicly accessible without delay the assessment report, 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 indication applied for.”

8. The following Article 21a is inserted:

“Article 21a

A marketing authorisation may be granted subject to one or more of the following conditions:

- (1) to take certain measures for the safe use of the medicinal product contained in the risk management system;
- (2) to conduct post-authorisation safety studies;
- (3) to comply with requirements on adverse reaction recording or reporting which are stricter than those referred to in Title IX;
- (4) any other conditions or restrictions with regard to the safe and effective use of the medicinal product.

The marketing authorisation shall lay down deadlines for the fulfilment of the conditions where necessary. “

9. Article 22 is replaced by the following:

“Article 22

In exceptional circumstances and following consultation with the applicant, the authorisation may be granted subject to a requirement for the applicant to meet certain

conditions, in particular concerning the safety of the medicinal product, notification to the national competent authorities of any incident relating to its use, and action to be taken.

This authorisation may be granted only when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I.

Continuation of the authorisation shall be linked to the annual reassessment of these conditions.”

10. The following Articles 22a and 22b are inserted:

“Article 22a

1. After the granting of a marketing authorisation, the national competent authority may require a marketing authorisation holder to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product. The requirement shall be made in writing, provide a detailed justification and include the objectives and timeframe for submission and conduct of the study.

2. The national competent authority shall provide the marketing authorisation holder with an opportunity to present explanations on the requirement within a time limit which it shall specify, if the marketing authorisation holder requests this within 30-days of receipt of the written requirement.

3. On the basis of explanations submitted by the marketing authorisation holder, the national competent authority shall withdraw or confirm the requirement. Where the national competent authority confirms the requirement, the marketing authorisation shall be varied to include the requirement as a condition of the marketing authorisation and the risk management system shall be updated accordingly.

Article 22b

1. The marketing authorisation holder shall be required to incorporate any conditions or requirements referred to in Articles 21a, 22 or 22a in his risk management system.

2. The Member States shall inform the Agency of the marketing authorisations that they have granted subject to conditions or requirements pursuant to Articles 21a, 22 or 22a.

The Agency shall include the medicinal products concerned in the list referred to in Article 23 of Regulation (EC) No 726/2004. The Agency shall remove a medicinal product from the list when the national competent authority concludes that the conditions or requirements have been fulfilled and that, following the assessment of any data resulting from the implementation of the conditions or requirements, the risk-benefit balance remains positive.”

11. Article 23 is replaced by the following:

“Article 23

1. After an authorisation has been granted, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in Article

8(3)(d) and (h), take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Those changes shall be subject to the approval of the competent authority of the Member State concerned.

2. The marketing authorisation holder shall forthwith supply to the national competent authority any new information which might entail the amendment of the particulars or documents referred to in Articles 8(3), 10, 10a, 10b and 11, or 32(5), or Annex I.

In particular, he shall forthwith inform the national competent authority of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product for human use is marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product for human use concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorisation, as well as data on the use of the medicinal product where such use is not in accordance with the summary of the product characteristics.

3. The marketing authorisation holder shall ensure that the product information is kept up to date with the current scientific knowledge including the assessment conclusions and recommendations made public by means of the European medicines safety web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004.
4. In order that the risk-benefit balance may be continuously assessed, the national competent authority may at any time ask the holder of the marketing authorisation to forward data demonstrating that the risk-benefit balance remains favourable.

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

12. Article 24 is amended as follows:

(a) In paragraph 2, the second subparagraph is replaced by the following:

“To this end, the marketing authorisation holder shall provide the national competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including the evaluation of data contained in adverse reactions reports and periodic safety update reports submitted in accordance with Title IX, and all variations introduced since

the marketing authorisation was granted, at least nine months before the marketing authorisation ceases to be valid in accordance with paragraph 1.”

(b) Paragraph 3 is replaced by the following:

“3. Once renewed, the marketing authorisation shall be valid for an unlimited period, unless the national competent authority decides, on justified grounds relating to pharmacovigilance or to insufficient exposure to the product, to proceed with one additional five-year renewal in accordance with paragraph 2.”

13. The title "Chapter 4 Mutual recognition and decentralised procedure" is deleted.

14. Article 27 is amended as follows:

(a) Paragraph 1 is replaced by the following:

“1. A coordination group shall be set up for the following purposes:

(a) the examination of any question relating to a marketing authorisation of a medicinal product in two or more Member States in accordance with the procedures laid down in Chapter 4;

(b) the examination of questions related to the pharmacovigilance of medicinal products authorised by the Member States, in accordance with Articles 107c, 107e, 107g, 107l and 107r;

(c) the examination of questions related to the variations to the terms of marketing authorisations granted by the Member States, in accordance with Article 35(1).

The Agency shall provide the secretariat of this coordination group.

For the fulfilment of its pharmacovigilance tasks, the coordination group shall be assisted by the Pharmacovigilance Risk Assessment Advisory Committee referred to in Article 56(1)(aa) of Regulation (EC) No 726/2004.”

(b) In paragraph 2, the following subparagraphs are added:

“Members of the coordination group and experts shall, for the fulfilment of their tasks, rely on the scientific and regulatory resources available to national marketing authorisation bodies. Each national competent authority shall monitor the level of expertise of the evaluations carried out and facilitate the activities of nominated coordination group members and experts.

Article 63 of Regulation (EC) No 726/2004 shall apply to the coordination group as regards the transparency and independence of its members.”

(c) The following paragraphs 4, 5, 6 and 7 are added:

“4. The Executive Director of the Agency or his representative 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 national competent authorities, including the consultative bodies concerned with the marketing authorisation.

6. Save where otherwise provided for in this Directive, the coordination group shall use its best endeavours to take decisions by consensus. If such a consensus cannot be reached, the position of the majority of members 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.”

15. After Article 27 the following is inserted:

“Chapter 4 Mutual recognition and decentralised procedure”

16. Article 31(1) is amended as follows:

(a) the first subparagraph is replaced by the following:

“The Member States or the Commission or the applicant or the marketing authorisation holder shall, in specific cases where the interests of the Community are involved, refer the matter to the Committee for application of the procedure laid down in Articles 32, 33 and 34 before any decision is reached on a request for a marketing authorisation or on the suspension or revocation of an authorisation, or on any other variation to the terms of a marketing authorisation which appears necessary.”

(b) the following subparagraph is inserted after the first subparagraph:

“However, where one of the criteria listed in Article 107i(1) is met, the procedure laid down in Articles 107i to 107l shall apply.”

17. In Article 36(1) the following subparagraph is added:

“However, where one of the criteria listed in Article 107i(1) is met, the procedure laid down in Articles 107i to 107l shall apply.”

18. Article 59(1) is amended as follows:

(a) the following point (aa) is inserted:

“(aa) a summary of the essential information necessary to use the medicine safely and effectively;”

(b) the following second and third subparagraphs are added:

“The information referred to in point (aa) of the first subparagraph shall be presented in a box surrounded by a black border. Any new or amended text shall for a period of 1-year be presented in bold text and preceded by the following symbol ****** and text "New information".

For medicinal products included on the list referred to in Article 23 of Regulation (EC) No 726/2004, the following additional statement shall be included “This medicinal product is under intensive monitoring. All suspected adverse reactions should be reported to <name and web-address of the national competent authority>”.

19. Article 63(3) is replaced by the following:

‘3. When the product is not intended to be delivered directly to the patient, or when the product is necessary to address severe availability problems, the competent authorities may, subject to measures they consider necessary to safeguard human health, grant an exemption to the obligation that certain particulars should appear on the labelling and in the package leaflet and that the leaflet must be in the official language or languages of the Member State in which the product is placed on the market.’

20. In Article 65, the following point (g) is added:

“(g) the summary of the essential information necessary to use the medicine safely and effectively provided for in Article 11(3a) and Article 59(1)(aa).”

21. Title IX is replaced by the following:

*“TITLE IX
PHARMACOVIGILANCE*

**CHAPTER 1
General provisions**

Article 101

1. Member States shall operate a pharmacovigilance system for the fulfilment of their pharmacovigilance tasks and their participation in Community pharmacovigilance activities.

The pharmacovigilance system shall be used to collect information on the risks of medicinal products as regards patients' or public health. That information shall particularly refer to adverse reactions in human beings, arising from use of the product within the terms of the marketing authorisation as well as from any other use, including overdose, misuse, abuse, medication errors, and those occurring in the course of studies with the medicinal product or after 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 as necessary. They shall perform a regular audit of their pharmacovigilance system and report the results to the Commission on [insert concrete date - two-years after the date of transposition referred to in Article 3(1)] at the latest and then every two years thereafter.

3. Each Member State shall designate a competent authority for the conduct of pharmacovigilance tasks.

4. The Commission may request Member States to participate, under the coordination of the Agency, in international harmonization and standardization of technical measures in pharmacovigilance.

Article 102

The Member States shall:

- (1) take all appropriate measures to encourage doctors, pharmacists and other health-care professionals to report suspected adverse reactions to the national competent authority or the marketing authorisation holder;

- (2) ensure that adverse reaction reports contain the highest quality information possible;
- (3) through the methods of collecting information and where necessary through the follow up of adverse reaction reports, ensure that any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of an adverse reaction report is identifiable;
- (4) take the necessary measures to ensure that a marketing authorisation holder who fails to discharge the obligations laid down in this Title is subject to effective, proportionate and dissuasive penalties.

For the purposes of point (1) of the first paragraph the Member States may impose specific requirements on doctors, pharmacists and other health-care professionals in respect of the reporting of suspected serious or unexpected adverse reactions.

Article 103

A Member State may delegate any of the tasks entrusted to it under this Title to another Member State subject to a written agreement of the latter.

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 public.

Article 104

1. The marketing authorisation holder shall be required to operate a pharmacovigilance system for the fulfilment of his pharmacovigilance tasks equivalent to the system under Article 101(1).

2. The marketing authorisation holder shall by means of the system referred to in paragraph 1 evaluate all information scientifically, consider options for risk minimisation and prevention and take appropriate measures as necessary.

The marketing authorisation holder shall be required to perform a regular audit of his pharmacovigilance system. He 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 followed.

3. As part of the pharmacovigilance system, the marketing authorisation holder shall be required to:

- (a) have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance;
- (b) maintain and make available on request a pharmacovigilance system master file;
- (c) operate a risk management system for each medicinal product;
- (d) monitor the outcome of risk minimization measures which are contained in the risk management plan or which are laid down as conditions or requirements in the marketing authorisation pursuant to Articles 21a, 22 or 22a;
- (e) assess updates to the risk management system and monitor pharmacovigilance data to determine whether there are new or changed risks or whether there are changes to the benefit-risk balance of medicinal products.

The qualified person referred to in point (a) of the first subparagraph shall reside in the Community 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 and the Agency.

Article 104a

1. By way of derogation from point (c) of Article 104(3), holders of marketing authorisations granted before [insert concrete date - date set out in the second subparagraph of Article 3(1) of Directive .../.../EC] shall be required to operate a risk management system only if paragraphs 2, 3 and 4 of this Article are complied with.
2. The national competent authority may require a marketing authorisation holder to operate a risk management system, as referred to in point (c) of Article 104(3), if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. To this effect, the national competent authority shall also require the marketing authorisation holder to submit a detailed description of the risk-management system which he intends to introduce for the medicinal product concerned.

The requirement shall be made in writing, provide a detailed justification, and include the timeframe for submission of the detailed description of the risk-management system.

3. The national competent authority shall provide the marketing authorisation holder with an opportunity to present explanations on the requirement within a

time limit which it shall specify, if the marketing authorisation holder requests this within 30 days of receipt of the written requirement.

4. On the basis of explanations submitted by the marketing authorisation holder, the national competent authority shall withdraw or confirm the requirement. Where the national competent authority confirms the requirement, the marketing authorisation shall be varied as appropriate to include measures of the risk management system as conditions of the marketing authorisation as referred to in point 1 of Article 21a.

Article 105

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 national competent authorities in order to guarantee their independence.

The first paragraph shall not preclude the collection of fees to be paid by marketing authorisation holders for the carrying out of those activities by the national competent authorities.

CHAPTER 2

Transparency and communications

Article 106

Each Member State shall set up and maintain a national medicines safety web-portal which shall be linked to the European medicines safety web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004. By means of the national medicines safety web-portals, the Member States shall make public at least the following:

- (1) risk management systems for medicinal products authorised in accordance with this Directive;
- (2) the list of medicinal products under intensive monitoring referred to in Article 23 of Regulation (EC) No 726/2004;
- (3) web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and patients based on the forms referred to in Article 25 of Regulation (EC) No 726/2004.

Article 106a

1. As soon as the marketing authorisation holder has the intention to make a public announcement relating to information on pharmacovigilance concerns to the use of a product, and in any event before the public announcement is made, he shall be required to inform the Member State competent authorities, the Agency and the Commission.

The marketing authorisation holder shall be required to ensure that information to the public is presented objectively and is not misleading.

2. 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 twenty-four hours prior to a public announcement relating to information on pharmacovigilance concerns.

3. For active substances contained in medicinal products authorised in more than one Member State, the Agency shall be responsible for the coordination between national competent authorities of safety announcements and shall provide timetables for the information being made public.

Under the coordination of the Agency, the Member States shall make all reasonable efforts to agree on common safety messages and the timetables for their distribution. The Pharmacovigilance Risk Assessment Advisory Committee shall, at the request of the Agency, provide advice on those safety announcements.

4. When the Agency or national competent authorities make information referred to in paragraphs 2 and 3 public, any information of a personal or commercially confidential nature shall be deleted unless its public disclosure is necessary for the protection of public health.

CHAPTER 3

Recording, reporting and assessment of pharmacovigilance data

Section 1

Recording and reporting of adverse reactions

Article 107

1. Marketing authorisation holders shall be required to record all suspected adverse reactions in the Community or in third countries which are brought to their attention,

whether reported spontaneously by patients or healthcare professionals or occurring in the context of a post-authorisation safety study.

Marketing authorisation holders shall be required to ensure that those reports are accessible at a single point within the Community.

By way of derogation to the first subparagraph, suspected adverse reactions occurring in the context of a clinical trial shall be recorded and reported in accordance with Directive 2001/20/EC.

2. The marketing authorisation holder may not refuse reports of suspected adverse reactions received electronically from patients and health-care professionals.

3. Marketing authorisation holders shall be required to submit electronically to the database and data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as ‘the Eudravigilance database’) information on all serious suspected adverse reactions that occur in the Community and in third countries within 15 days following the receipt of the report or, in the absence of a report, following the day on which the holder concerned gained knowledge of the event.

Marketing authorisation holders shall be required to submit electronically to the Eudravigilance database information on all non-serious suspected adverse reactions that occur in the Community, within 90 days following the receipt of the report or, in the absence of a report, following the day on which the holder concerned gained knowledge of the event.

For medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to Article 27 of 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 medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions.

4. Member States shall access reports on adverse reactions through the Eudravigilance database and shall assess the quality of the data received from marketing authorisation holders. They shall, as appropriate, involve patients and health-care professionals in the follow up of any reports they receive and request follow up of such reports to be conducted by the marketing authorisation holders. The marketing authorisation holders shall be required to report any follow up information received to the Eudravigilance database.

Article 107a

1. The Member States shall record all suspected adverse reactions that occur in their territory which are brought to their attention from healthcare professionals and patients.

Member States shall ensure that reports of such reactions are submitted by means of the national medicines safety web-portals.

2. Member States shall, within 15 days following the receipt of the reports referred to in paragraph 1, submit the reports electronically to the Eudravigilance database.

Marketing authorisation holders shall access those reports through the Eudravigilance database.

3. The Member States shall ensure that reports of medication errors brought to their attention in the framework of suspected adverse reaction reporting for medicinal products are made available to the Eudravigilance database and to any authorities responsible for patient safety within that Member State. 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 the authorities responsible for patient safety within that Member State.

Section 2

Periodic safety update reports

Article 107b

1. Marketing authorisation holders shall be required to submit to the Agency periodic safety update reports containing:

- (a) summaries of data relevant to the benefits and risks of the medicinal product;
- (b) a scientific evaluation of the risk-benefit 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.

The evaluation referred to in point (b) shall be based on all available data, including data from clinical trials in unauthorised indications and populations.

The periodic safety update reports shall be submitted electronically.

2. The Agency shall distribute the reports referred to in paragraph 1 to the Pharmacovigilance Risk Assessment Advisory Committee, the Committee for Medicinal Products for Human Use and the coordination group.

3. By way of derogation from paragraph 1 of this Article, holders of marketing authorisations for medicinal products referred to in Articles 10, 10a or 10c, and holders of registrations for medicinal products referred to in Articles 14 or 16a, shall be required to submit periodic safety update reports for such products only in the following cases:

- (a) where such obligation has been laid down as a condition in the marketing authorisation in accordance with Article 21a or Article 22; or
- (b) where a Community reference date and the corresponding frequency of submission of periodic safety update reports have been determined in accordance with paragraphs 3 and 4 of Article 107c, subject to the conditions laid down in Article 107c(5).

Article 107c

1. The frequency of submission of the periodic safety update reports shall be specified in the marketing authorisation.

It shall be counted from the date of the authorisation.

2. Holders of marketing authorisations which were granted before [insert concrete date - date set out in the second subparagraph of Article 3(1)], and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the marketing authorisation, shall submit the periodic safety update reports in accordance with the second subparagraph of this paragraph until another frequency or other dates of submission of the reports are laid down in the marketing authorisation or determined in accordance with paragraphs 3, 4, 5 or 6..

Periodic safety update reports shall be submitted to the competent authorities immediately upon request or in accordance with the following:

- (a) where a product has not yet been placed on the market, at least every six months after authorisation and until the placing on the market;
- (b) where a 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. Where products that are subject to different marketing authorisations contain the same active substance or combination thereof, the frequency and dates of submission of the periodic safety update reports resulting from the application of paragraphs 1 and 2 may

be amended to provide for a single frequency for the submission of the reports relating to all such products and to provide for a Community reference date from which the frequency is counted.

This single frequency for the submission of the reports and the Community reference date may be determined, after consultation of the Pharmacovigilance Risk Assessment Advisory 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 procedure of Regulation (EC) No 726/2004;
- (b) the coordination group, in other cases than those referred to in point (a).

4. For the purposes of paragraph 3, the Community reference date for products containing the same active substance or combination thereof shall be one of the following:

- (a) the date of the first authorisation in the Community of a medicinal product containing that active substance or combination;
- (b) if the date referred to in point (a) cannot be ascertained, the earliest of the known dates of the marketing authorisations for medicinal product containing that active substance or combination.

5. When establishing Community reference dates and the frequency of submission of periodic safety update reports, or subsequently, the Committee for Medicinal Products for Human Use or the coordination group, as appropriate, may require that periodic safety update reports are also submitted for medicinal products referred to in Article 107b(3), under the following conditions:

- (a) the obligation to submit the reports shall apply for a specific period determined by the Committee or the coordination group, as appropriate; and
- (b) the obligation shall be based on one of the following grounds relating to the protection or promotion of public health:
 - (i) evidence is available that product information relating to the safe use of the medicinal products concerned is out of date;
 - (ii) a need to update warnings in product information based on new information has been identified.

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 Community reference dates or to change the frequency of submission periodic safety update reports on one of the following grounds:

- (a) for reasons related to public health;
- (b) in order to avoid duplication of assessment;
- (c) in order to achieve international harmonisation.

Such requests shall be submitted in writing and shall be duly justified.

7. The Agency shall make public a list of Community reference dates and frequency of submission of periodic safety update reports by means of the European medicines safety 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 paragraphs 3, 4, 5 and 6 shall take effect six months after the date of such publication.

Article 107d

The national competent authorities shall assess periodic safety update reports to determine whether there are new or changed risks or whether there are changes to the risk benefit balance of medicinal products.

Article 107e

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 of paragraphs 3 to 6 of Article 107c, for all medicinal products containing the same active substance or combination thereof and for which a Community reference date and frequency of periodic safety update reports has been established.

The 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 procedure of Regulation (EC) No 726/2004;
- (b) a rapporteur appointed by the Pharmacovigilance Risk Assessment Advisory Committee, where at least one of the marketing authorisations concerned has been granted in accordance with the procedure of Regulation (EC) No 726/2004.

When selecting the Member State in accordance with point (a) of the second subparagraph, the coordination group shall take into account whether any Member State is acting as a reference Member State, in accordance with Article 28(1).

2. The Member State or rapporteur, as appropriate, shall prepare an assessment report within 90 days of receipt of the periodic safety update report and send it to the marketing authorisation holder and the Pharmacovigilance Risk Assessment Advisory Committee.

Within 30 days of receipt of the assessment report, the marketing authorisation holder may submit comments to the Agency. The Agency shall make such comments available to the Member State or rapporteur and to the Pharmacovigilance Risk Assessment Advisory Committee.

3. At its next meeting following the end of the period for comments by the marketing authorisation holder referred to in paragraph 2, the Pharmacovigilance Risk Assessment Advisory Committee shall adopt the assessment report with or without changes, taking into account any comments submitted in accordance with that paragraph.

Article 107f

Following the assessment of periodic safety update reports, the national competent authorities shall consider whether any action concerning the terms of the marketing authorisation for the medicinal product concerned is necessary.

They shall maintain, vary, suspend or revoke the marketing authorisation as appropriate.

Article 107g

1. In the case of a single assessment of periodic safety update reports concerning more than one marketing authorisation in accordance with Article 107e(1) which does not include any marketing authorisation granted in accordance with Regulation (EC) No 726/2004, the coordination group shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Advisory 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.

2. If the opinion of the coordination group is adopted by consensus, the chairman shall record the agreement and inform the marketing authorisation holder accordingly. The Member States shall maintain, vary, suspend or revoke the marketing authorisations concerned as necessary to comply with the opinion within the determined time table for implementation, and they shall inform the Commission and the coordination group.

If an opinion by consensus cannot be adopted, the majority opinion shall be forwarded to the Commission which shall apply the procedure laid down in Articles 33 and 34.

3. In the case of a single assessment of periodic safety update reports concerning more than one marketing authorisation in accordance with Article 107e(1) which includes at least one marketing authorisation granted in accordance with the procedure of Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall, within 30 days of receipt of the report of the Pharmacovigilance Risk Assessment Advisory Committee, consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisations concerned.

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall:

- (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 under this section; and
- (b) where the opinion states that regulatory action is necessary, adopt a decision to vary, suspend or revoke the marketing authorisations granted in accordance with Regulation (EC) No 726/2004 and concerned by the procedure under this section.

Articles 33 and 34 of this Directive shall apply to the adoption of the decision referred to in point (a) of the first subparagraph of this paragraph and to its implementation by the Member States.

Article 10 of Regulation (EC) No 726/2004 shall apply to the decision referred to in point (b) of the first subparagraph of this paragraph. Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of this Directive.

Article 107h

1. Regarding medicinal products authorised in accordance with this Directive, the Agency and national competent authorities shall take the following measures:

- (a) monitor the outcome of risk minimization measures contained in risk management systems and of conditions or requirements referred to in Articles 21a, 22 or 22a;
- (b) assess updates to the risk management system;

- (c) monitor the data in the Eudravigilance database to determine whether there are new or changed risks or whether there are changes to the risk benefit balance.

Member States shall ensure that the marketing authorisation holders also take the measures set out in points (a), (b) and (c).

2. The Pharmacovigilance Risk Assessment Advisory Committee shall perform the initial scrutiny and prioritisation of indications of new or changing risks or changes to the risk-benefit balance. Where it considers that follow-up action may be necessary, the assessment of those indications and any subsequent action as regards the marketing authorisation shall be conducted in accordance with Articles 107d to 107g.

3. The Agency and national competent authorities shall inform each other and the marketing authorisation holder in the event of new or changed risks or changes to the risk benefit balance being detected.

Member States shall ensure that marketing authorisation holders inform the Agency and national competent authorities in the event of new or changed risks or changes to the risk benefit balance being detected.

Section 3 **Community procedure**

Article 107i

1. A Member State shall initiate the procedure under this section, by informing the other Member States, the Agency and the Commission, in any of the following cases:

- (a) it considers suspending or revoking of a marketing authorisation;
- (b) it considers prohibiting the supply of a medicinal product;
- (c) it considers refusing the renewal of a marketing authorisation;
- (d) it is informed by the marketing authorisation holder that, on the basis of safety concerns, he has interrupted the placing on the market of a medicinal product or withdrawn a marketing authorisation, or that he intends to do so;
- (e) it considers that new contraindications, a reduction in the recommended dose, or a restriction to the indications is necessary;

- (f) it has conducted a pharmacovigilance inspection and found serious deficiencies.

2. The information referred to in paragraph 1 may relate to individual medicinal products or to a range of medicinal products or a therapeutic class.

If the Agency identifies that the issue relates to more medicinal products than those which are covered by the information or that it is common to all products belonging to the same range or therapeutic class, it shall extend the scope of the procedure accordingly.

Where the scope of the procedure initiated under this section concerns a range of products or therapeutic class, medicinal products authorised in accordance with Regulation (EC) No 726/2004 which belong to that range or class shall also be included in the procedure.

3. At the time of the information referred to in paragraph 1, the Member State shall make available to the Agency all relevant scientific information available to it and any assessment by the Member State.

Article 107j

1. After initiation of the procedure under this section, where urgent action to protect public health is necessary, the Member State concerned may suspend the marketing authorisation or prohibit the use of a medicinal product. It shall inform the Agency, the Commission and the other Member States not later than the following working day.

2. At any stage of the procedure under this section, the Commission may request the Member States in which the product is authorised to take temporary measures immediately.

3. Where the scope of the procedure, as determined in accordance with Article 107i(2), concerns a range of products or therapeutic class which includes medicinal products authorised in accordance with Regulation (EC) No 726/2004 the Commission may at any stage of the procedure initiated under this section take temporary measures immediately in relation to those marketing authorisations.

Article 107k

1. Following the information referred to in Article 107i(1), the Agency shall publicly announce the initiation of the procedure by means of the European medicines safety web-portal.

The announcement shall specify the matter submitted, the medicinal products and, where applicable, the substances concerned. It shall contain information on the right of the marketing authorisation holders 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 Advisory Committee shall assess the matter which has been submitted. For the purposes of that assessment, it may hold a public hearing.

Public hearings shall be announced by means of the European medicines safety web-portal. The announcement shall include information on how marketing authorisation holders and the public can participate.

The Agency shall provide the opportunity, to all those who request it, to participate in the hearing either in person or through the use of web-based technology.

Where a marketing authorisation holder or another person intending to submit information has commercially confidential data relevant to the issue of the procedure, he may request to present those data to the Pharmacovigilance Risk Assessment Advisory Committee in a non-public hearing.

3. Within 60 days of the information submitted, the Pharmacovigilance Risk Assessment Advisory Committee shall make a recommendation, stating the reasons on which it is based. The recommendation shall be any or a combination of the following:

- (a) no further evaluation or action is required at Community level;
- (b) the marketing authorisation holder should conduct further evaluation of data together with the follow up of the results of that evaluation;
- (c) the marketing authorisation holder should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study;
- (d) the Member States or marketing authorisation holders should implement risk minimisation measures;
- (e) the marketing authorisation should be suspended, revoked or not renewed;
- (f) the marketing authorisation should be varied.

For the purposes of point (d) of the first subparagraph, the recommendation shall specify the risk minimisation measures recommended and any conditions or restrictions to which the marketing authorisation should be made subject.

Where, in the cases referred to in point (f) of the first subparagraph, 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 where such wording should be placed in the summary of the product characteristics, labelling or package leaflet.

Article 107l

1. Where the scope of the procedure, as determined in accordance with Article 107i(2), does not include any marketing authorisation granted in accordance with the procedure of Regulation (EC) No 726/2004, the coordination group shall, within 30 days of the recommendation of the Pharmacovigilance Risk Assessment Advisory Committee, consider the recommendation and adopt an opinion on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisations concerned, including a timetable for the implementation of the opinion.

2. If the opinion of the coordination group is adopted by consensus, the chairman shall record the agreement and inform the marketing authorisation holder accordingly. The Member States shall maintain, vary, suspend, revoke or refuse renewal of the marketing authorisation as necessary to comply with the opinion within the determined time table for implementation, and they shall inform the Commission and the coordination group.

If an opinion by consensus cannot be adopted, the majority opinion shall be forwarded to the Commission which shall apply the procedure laid down in Articles 33 and 34. However, by way of derogation from Article 34(1), the procedure referred to in Article 121(2) shall apply.

3. Where the scope of the procedure, as determined in accordance with Article 107i(2), includes at least one marketing authorisation granted in accordance with the procedure of Regulation (EC) No 726/2004, the Committee for Medicinal Products for Human Use shall, within 30 days of the recommendation of the Pharmacovigilance Risk Assessment Advisory Committee, consider the recommendation and adopt an opinion on the maintenance, variation, suspension, revocation or refusal of the renewal of the marketing authorisations concerned.

4. On the basis of the opinion of the Committee for Medicinal Products for Human Use referred to in paragraph 3, the Commission shall:

- (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 under this section; and

- (b) where the opinion is that regulatory action is necessary, adopt a decision to vary, suspend, revoke or refuse renewal of the marketing authorisations granted in accordance with Regulation (EC) No 726/2004 and concerned by the procedure under this section.

Articles 33 and 34 of this Directive shall apply to the adoption of the decision referred to in point (a) of the first subparagraph of this paragraph and to its implementation by the Member States. However, by way of derogation from Article 34(1) of this Directive, the procedure referred to in Article 121(2) thereof shall apply.

Article 10 of Regulation (EC) No 726/2004 shall apply to the decision referred to in point (b) of the first subparagraph of this paragraph. However, by way of derogation from Article 10(2) of that Regulation, the procedure referred to in Article 87(2) thereof shall apply. Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of this Directive.

Section 4 **Publication of assessments**

Article 107m

The Agency shall make public the recommendations, opinions and decisions referred to in Articles 107b to 107l by means of the European medicines safety web-portal.

CHAPTER 4 **Supervision of post-authorisation safety studies**

Article 107n

1. This Chapter shall apply to non-interventional post-authorisation safety studies which are initiated, managed or financed by the marketing authorisation holder, voluntarily or following a requirement in accordance with Articles 21a or 22a, and which involve the collection of data from patients or health-care professionals.

2. The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.

Article 107o

1. Before a study is conducted, the marketing authorisation holder shall be required to submit a draft protocol to the national competent authority, for studies to be conducted in only one Member State, and to the Pharmacovigilance Risk Assessment Advisory Committee, for studies to be conducted in more than one Member State.

2. Within 60 days of the submission of the draft protocol the national competent authority or the Pharmacovigilance Risk Assessment Advisory Committee, as appropriate, may issue

- (a) a letter of objection, which shall be based on detailed grounds, in any of the following cases:
 - (i) it considers that the study is a clinical trial falling under the scope of Directive 2001/20/EC;
 - (ii) it considers that the conduct of the study promotes the use of a medicinal product;
 - (iii) it considers that the design of the study does not fulfil the study objectives; or
- (b) a recommendation on the draft protocol.

3. After the expiry of the period referred to in paragraph 2 the marketing authorisation holder may commence the study. However, where a letter of objection referred to in point (a) of paragraph 2 has been issued, the study may commence only with the written approval from the national competent authority or the Pharmacovigilance Risk Assessment Advisory Committee, as appropriate.

Where a recommendation referred to in point (b) of paragraph 2 has been issued, the marketing authorisation holder shall take that recommendation into account before commencing the study.

Article 107p

1. After a study has been commenced, major amendments to the protocol shall be submitted to the national competent authority or the Pharmacovigilance Risk Assessment Advisory Committee, as appropriate.

2. During the conduct of a study, the marketing authorisation holder shall continuously monitor the data generated and its implications for the risk-benefit balance of the medicinal product concerned.

Any new information which might influence the risk-benefit balance of the medicinal product shall be communicated to the national competent authority in accordance with Article 23.

3. Payments to healthcare professionals for participating in the studies shall be restricted to compensation of time and expenses incurred.

Article 107q

1. Upon completion of the study, final study reports shall be submitted to the national competent authority or the Pharmacovigilance Risk Assessment Advisory Committee within 12 months of the last patient visit unless a written waiver has been given by the national competent authority or the Pharmacovigilance Risk Assessment Advisory Committee, as appropriate.

2. The marketing authorisation holder shall consider whether the results of the study have an impact on the terms of the marketing authorisation and shall if necessary submit to the national competent authorities an application to vary the marketing authorisation.

3. The marketing authorisation holder shall electronically submit an abstract of the study results to the national competent authority or the Pharmacovigilance Risk Assessment Advisory Committee.

For studies conducted in more than one Member State, the Pharmacovigilance Risk Assessment Advisory Committee may decide that the abstract is made public by means of the European medicines safety web-portal, after deletion of any information of a commercially confidential nature.

Article 107r

1. Based on the results of the study and after consultation of the marketing authorisation holder, the Pharmacovigilance Risk Assessment Advisory Committee may make recommendations concerning the terms of the marketing authorisation, stating the reasons on which they are based. Those recommendations shall be made public by means of the European medicines safety web-portal.

2. When recommendations for the variation, suspension or revocation of the marketing authorisation are made for a medicinal product authorised by the Member States pursuant to this Directive, the coordination group shall adopt an opinion on the matter taking into account the recommendation referred to in paragraph 1 and including a timetable for the implementation of the opinion.

If the opinion of the coordination group is adopted by consensus, the chairman shall record the agreement and inform the marketing authorisation holder accordingly. The Member States shall vary, suspend or revoke the marketing authorisation concerned as necessary to comply with the opinion within the determined time table for implementation, and they shall inform the Commission and the coordination group.

If an opinion by consensus cannot be adopted, the majority opinion shall be forwarded to the Commission which shall apply the procedure laid down in Articles 33 and 34.

CHAPTER 5

Guidelines, adaptation and review

Article 108

Following consultation with the Agency, Member States and interested parties, the Commission shall adopt and make public guidelines on good pharmacovigilance practice for medicinal products authorised in accordance with Article 6(1) in the following areas:

- (1) the establishment and operation of the pharmacovigilance system by the marketing authorisation holder and the content and maintenance of the pharmacovigilance system master file;
- (2) quality assurance and quality control by the marketing authorisation holder, the national competent authorities and the Agency of their performance of pharmacovigilance activities.
- (3) the use of internationally agreed terminologies, formats and standards for the conduct of pharmacovigilance;
- (4) the methodology for the monitoring of data in the Eudravigilance database to determine whether there are new or changed risks;
- (5) the format of electronic reporting of adverse reactions by Member States and marketing authorisation holders;
- (6) the format of electronic periodic safety update reports;
- (7) the format of protocols, abstracts and final study reports for the post-authorisation safety studies;
- (8) the procedures and formats for pharmacovigilance communications.

Those guidelines shall take account of international harmonisation work carried out in the field of pharmacovigilance and shall where necessary be revised to take account of technical and scientific progress.

Article 108a

The Commission shall adopt any amendments which may be necessary to update the provisions of this Title to take account of scientific and technical progress.

Those measures, designed to amend non-essential elements of this Directive, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 121(2a).

Article 108b

The Commission shall make public a report on the conduct of pharmacovigilance tasks by the Member States on [insert concrete date: three-years after the date of transposition referred to in Article 3(1)] at the latest and then every three years thereafter.”

22. Article 111 is amended as follows:

(a) paragraph 1 is amended as follows:

(i) the first subparagraph is replaced by the following:

“Under the coordination of the Agency, the competent authority of the Member State concerned shall ensure that the legal requirements governing medicinal products are complied with, by means of repeated inspections, and if necessary unannounced inspections, and, where appropriate, by asking an Official Medicines Control Laboratory or a laboratory designated for that purpose to carry out tests on samples. ”

(ii) In the fifth subparagraph point (d) is replaced by the following:

“(d) inspect the premises, records, documents and pharmacovigilance system master file of marketing authorisation holders or any firms employed by the marketing authorisation holder to perform the activities described in Title IX.”

(b) Paragraph 3 is replaced by the following:

“3. After every inspection as referred to in paragraph 1, the competent authority shall report on whether the manufacturer, importer or wholesaler complies with the principles and guidelines of good manufacturing practice and good distribution practice referred to

in Articles 47 and 84, or on whether the marketing authorisation holder complies with the requirements laid down in Title IX.

The competent authority which carried out the inspection shall communicate the content of those reports to the manufacturer, importer, marketing authorisation holder, or wholesale distributor who has undergone the inspection.

Before adopting the report, the competent authority shall give the manufacturer, importer, marketing authorisation holder, or wholesale distributor concerned the opportunity to submit their comments.”

(c) Paragraph 7 is replaced by the following:

“7. If the outcome of the inspection as referred to in points (a), (b) and (c) of paragraph 1 is that the manufacturer does not comply with the principles and guidelines of good manufacturing practice as provided for by Community legislation, the information shall be entered in the Community database as referred to in paragraph 6.”

(d) The following paragraph 8 is added:

“8. If the outcome of the inspection as referred to in paragraph 1(d) is that the marketing authorisation holder does not comply with the pharmacovigilance system as described in the pharmacovigilance system master file and with Title IX, the competent authority of the Member State concerned shall bring the deficiencies to the attention of the marketing authorisation holder and give him the opportunity to submit his comments.

In such case the Member State concerned shall inform the other Member States, the Agency and the Commission.

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.”

23. Article 116 is replaced by the following:

“Article 116

The competent authorities shall suspend, revoke, withdraw or vary a marketing authorisation if the view is taken that the product is harmful or that it lacks therapeutic efficacy, or that the risk-benefit balance is not positive, 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.

An authorisation shall also be suspended, revoked, withdrawn or varied where the particulars supporting the application as provided for in Article 8 or Articles 10 to 11 are incorrect or have not been amended in accordance with Article 23, or where any conditions or requirements referred to in Articles 21a, 22 or 22a have not been fulfilled or where the controls referred to in Article 112 have not been carried out.”

24. Article 117 is amended as follows:

(a) paragraph 1 is amended as follows:

(i) point (a) in is replaced by the following:

“(a) the medicinal product is harmful; or”

(ii) point (c) is replaced by the following:

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

(b) The following paragraph 3 is added:

“3. The competent authority may prohibit the supply of the product to new patients.”

25. In Article 122(2) the following subparagraph is added:

“The Member States shall send electronically all inspection reports to the Agency. “

26. Article 123(4) is replaced by the following:

“4. The Agency shall make public annually a list of the medicinal products which are prohibited in the Community.”

27. In Article 126a, paragraphs 2 and 3 are replaced by the following:

‘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 Title V, with the exception of Article 63(1) and (2), and Titles VI, VIII, IX and XI.

3. Before granting such an authorization a Member State shall notify the marketing authorization holder, in the Member State in which the medicinal product concerned is authorised, of the proposal to grant an authorization under this Article in respect of the product concerned.’

28. Article 127a is replaced by the following:

“Article 127a

When a medicinal product is to be authorised in accordance with Regulation (EC) No 726/2004, and the Scientific Committee in its opinion refers to recommended conditions or restrictions as provided for in points (c), (ca) or (cb) of Article 9(4) thereof, the Commission may adopt a decision addressed to the Member States, in accordance with Articles 33 and 34 of this Directive, for the implementation of those conditions or restrictions.”

Article 2 *Transitional provisions*

1. With regard to the requirement for the inclusion of a summary of the essential information necessary to use the medicine safely and effectively in the summary of the product characteristics and the package leaflet provided for in point 3a of Article 11 and in point (aa) of Article 59(1) of Directive 2001/83/EC as amended by this Directive, the Member States shall ensure that the requirement applies to a marketing authorisation granted before the date set out in the second subparagraph of Article 3(1) of this Directive from renewal of that authorisation or from the expiry of a period of three years starting from that date, whichever is the earliest.
2. With regard to the requirement for the marketing authorisation holder to maintain and make available on request a pharmacovigilance system master file in respect of one or more medicinal products provided for in point (b) of Article 104(3) of Directive 2001/83/EC as amended by this Directive, the Member States shall ensure that that requirement applies to marketing authorisations granted before the date set out in the second subparagraph of Article 3(1) of this Directive or from the expiry of a period of three years starting from that date
3. The Member States shall ensure that the procedure under Articles 107n to 107r of Directive 2001/83/EC as amended by this Directive applies only to studies which have commenced after the date set out in the second subparagraph of Article 3(1) of this Directive.

Article 3 *Transposition*

1. Member States shall adopt and publish, by [18 months from the entry into force] at the latest, the laws, regulations and administrative provisions necessary to comply with this Directive. They shall forthwith communicate to the Commission the text of those provisions and a correlation table between those provisions and this Directive.

They shall apply those provisions from [18 months from the entry into force].

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

Article 4 *Entry into force*

This Directive shall enter into force on the twentieth day after that of its publication in the *Official Journal of the European Union*.

Article 5 *Addressees*

This Directive is addressed to the Member States.

Done at Brussels,

For the European Parliament
The President

For the Council
The President

LEGISLATIVE FINANCIAL STATEMENT

1. NAME OF THE PROPOSAL:

A Regulation amending Regulation (EC) 726/2004, and a Directive amending Directive 2001/83/EC on Pharmacovigilance.

2. ABM / ABB FRAMEWORK

Policy Area(s) concerned and associated Activity/Activities:

Policy area(s): Internal Market (Article 95 of the EC Treaty).

Activities:

- Improving the protection of public health across the Community in relation to the safety of medicinal products;
- Supporting the achievement of the internal market in the pharmaceutical sector;

3. BUDGET LINES

3.1. Budget lines (operational lines and related technical and administrative assistance lines (ex- B..A lines)) including headings:

02.030201 – European Medicines Agency — Subsidy under Titles 1 and 2

02.030202 – European Medicines Agency — Subsidy under Title 3

3.2. Duration of the action and of the financial impact:

The assumption is that the proposed package of a Regulation and Directive on Pharmacovigilance would apply from late 2011 (year "n"). The calculation in the Annex has been calculated for 2011-2016.

3.3. Budgetary characteristics:

Budget line	Type of expenditure		New	EFTA contribution	Contributions from applicant countries	Heading in financial perspective
02.030201	Non-comp	Non-diff ¹⁵	NO	YES	NO	No 1a0203
02.030202	Non-comp	Non-diff	NO	YES	NO	No 1a0203

4. SUMMARY OF RESOURCES

4.1. Financial Resources

4.1.1. Summary of commitment appropriations (CA) and payment appropriations (PA)

Not applicable

Co-financing details

Not applicable

4.1.2. Compatibility with Financial Programming

☒ Proposal is compatible with existing financial programming.

4.1.3. Financial impact on Revenue

☒ Proposal has no financial implications on revenue (see details of calculation in the Annex)

4.2. Human Resources FTE (including officials, temporary and external staff)

Not applicable.

5. CHARACTERISTICS AND OBJECTIVES

5.1. Need to be met in the short or long term

Significant weaknesses of the current EU system of pharmacovigilance have been identified through an independent Commission sponsored study, extensive public consultation (in 2006 and again in 2007) and through detailed analysis by the

¹⁵ Non-differentiated appropriations hereafter referred to as NDA.

Commission services. Taken together these problems mean that the safety of EU citizens is not optimally protected so that there is an opportunity to reduce the public health burden ADRs by improving EU pharmacovigilance.

5.2. Value-added of Community involvement and coherence of the proposal with other financial instruments and possible synergy

Considering existing EU legislation, functioning of the single market and the increasing share of centrally authorised medicinal products, action of Member States alone could not be sufficient to bring full harmonisation of pharmacovigilance rules between Member States and the objectives of this legal proposal can only be fully achieved at the Community level.

5.3. Objectives, expected results and related indicators of the proposal in the context of the ABM framework

The high level objective of the proposal is to improve the protection of public health in the Community while enhancing the single market in medicinal products, by strengthening and rationalising EU pharmacovigilance. This will be achieved through the operational objectives of:

- Providing for clear roles and responsibilities for the key responsible parties;
- Rationalising EU decision-making on drug safety issues;
- Strengthening medicines safety transparency and communication;
- Strengthen companies' pharmacovigilance systems;
- Ensure the proactive and proportionate collection of high quality data;
- Involve stakeholders in pharmacovigilance.

The proposal's objectives contribute to the strategic goals of the Community framework for the authorisation, supervision and surveillance of medicinal products i.e.:

- Ensuring that public health is adequately protected across the Community;
- Supporting the achievement of the internal market for the pharmaceutical sector.

5.4. Method of Implementation (indicative)

☒ ***Centralised Management***

☒ indirectly by delegation to:

- ☒ bodies set up by the Communities as referred to in art. 185 of the Financial Regulation

6. MONITORING AND EVALUATION

6.1. Monitoring system

The Commission has established mechanisms for working with the Member States to monitor transposition.

With regard to *ex-post* evaluation the following are considered relevant, accepted, credible, easy and robust:

- On clear roles and responsibilities and clear standards against which they perform their roles, a regular report by the European Commission, pharmacovigilance inspections and EMEA audit;
- On rationalising EU decision-making, the timing of the establishment of the new EMEA committee structure and the number of pharmacovigilance referrals to the EMEA;
- On transparency and communication, measure the establishment by Member States of medicines safety websites, the launch of the EU safety web-portal by the EMEA and evaluate the inclusion of information;
- On oversight of companies' pharmacovigilance systems - inspections;
- On proactive collection of high quality data, measure the number of risk management plans submitted and the concordance between the studies required;
- On reporting of adverse reactions, measure the number and quality of ADR and PSUR reports evaluated;
- On involving stakeholders in pharmacovigilance, measure the number and proportion of adverse reaction reports received from patients.

6.2. Evaluation

6.2.1. *Ex-ante* evaluation

During the impact assessment process the Commission services extensively consulted all relevant stakeholders using the whole range of communication means. Two general web-based public consultations were supplemented by questionnaire surveys and workshops with specific stakeholder groups. The Commission Pharmaceutical Committee, the EMEA scientific committees, and the Heads of EEA Medicines Agencies, have been

consulted. Concurrently comments of the Commission services raised during the inter-service steering group meetings were fully taken into consideration.

6.2.2. *Measures taken following an intermediate/ex-post evaluation (lessons learned from similar experiences in the past)*

The study “Assessment of the European Community System of Pharmacovigilance”¹⁶, aimed specifically to analyse how the European central and EU Member States' medicines agencies collaborate with each other, the marketing authorisation holders and other stakeholders in monitoring the adverse effects of pharmaceutical products and to put forward recommendations to make the system more robust.

6.2.3. *Terms and frequency of future evaluation*

It should be noted that the proposal specifically provides for a three-yearly report by the European Commission services on the operation of pharmacovigilance by the Member States, for pharmacovigilance inspections, and for EMEA audit.

The specific objective of improving public health protection through strengthening and rationalising EU pharmacovigilance can be measured by an external study.

The two EU legal acts that are being modified contain existing general review clauses (Commission report every 10-years) which will apply to the new provisions.

7. ANTI-FRAUD MEASURES

The European Medicines Agency has specific budgetary control mechanisms and procedures. The Management Board, which comprises representatives of the Member States, the Commission and the European Parliament, adopts the budget (Article 66(f) of Regulation (EC) No 726/2004), as well as the internal financial provisions (Article 66(g)). The European Court of Auditors examines the execution of the budget each year (Article 68.3).

Regarding fraud, corruption and other unlawful activities, the provisions of Regulation (EC) No 1073/1999 of the European Parliament and of the Council of 25 May 1999 concerning investigations conducted by the European Anti-Fraud Office (OLAF) apply to the EMEA without restriction. Besides, a decision concerning co-operation with the OLAF was already adopted on 1 June 1999 (EMEA/D/15007/99).

Finally, the Quality Management System applied by the Agency supports a continuous review, whose objective is to ensure that the correct procedures are followed and that these procedures and policies are pertinent and efficient. Several internal audits are undertaken each year as part of this process.

¹⁶

http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/docs/acs_consultation_final.pdf

ANNEX: details of calculation

Introduction

The Legislative Financial Statement is proposed based on the fact that the legislative proposals, if adopted, will enable for the first time, pharmacovigilance activities to be the subject of fees charged by the European Medicines Agency –EMA. The Legislative Financial Statement and the calculations in this annex demonstrate that all costs relating to activities resulting from the legislative proposal will be recuperated through fees. On this basis, the calculation in this Annex leads to the conclusion that the proposed measures are not expected to have a significant financial impact on the Community budget.

Pharmacovigilance and maintenance activities accounted for 13.5% of the Agency human resource (ca. 70 FTEs) and 14.54% of the Agency costs (€ 25.2 million including support service). The average cost of 1 full time equivalent (FTE) AD Staff Member for the EMA in London has been provided by the EMA (draft 2007 costs) as: Salary: €112.113 and Salary and overheads: €161.708.

The Community assessments would require payment of rapporteurs who would receive their payment through the Agency. We have assumed fees with 50% of the fee revenue retained by EMA and 50% paid to rapporteurs.

Fees charged by the EMA to the pharmaceutical industry

To support the pharmacovigilance provisions, the following fee estimates can be made:

	Community pharmacovigilance referrals	PSURs assessed	Community study assessments	Community risk management assessments
Number (year)	20	1000	300	100
Estimated fee	€72,800	€6,100	€6,100	€12,100
Total	20 x €72,800 = €1,456,000	1000 x €6,100 = €6,100,000	300 x €6,100 = €1,830,000	100 x €12,100 = €1,210,000

Based on the estimates above the additional annual income to the EMA from pharmacovigilance fee revenue will be €10,596,000.

Payments by the EMEA to rapporteurs for Community pharmacovigilance assessments

It is estimated that these scientific assessments by rapporteurs should be subject to payment of half the fee. On this basis the following payments by EMEA to rapporteurs can be estimated:

	Community pharmacovigilance referrals	PSURs assessed	Community study assessments	Community risk management assessments
Number (year)	20	1000	300	100
Estimated payment to rapporteur	€36,400	€3,050	€3,050	€6,050
Total	20 x €36,400 = €728,000	1000 x €3,050 = €3,050,000	300 x €3,050 = €915,000	100 x €6,050 = €605,000

Based on the estimates above the new costs to EMEA to pay for rapporteur assessments will be €6,230,100.

Literature monitoring:

On the basis of estimates from the EMEA (3 additional information analysts if the main function was outsourced) and from one private literature monitoring company¹⁷ (€533,333 annually for 3000 monitored substances, doubled to cover uncertainty relating to the number of substances and detailed processes), we can estimate the increase in costs to the EMEA of approximately €1.56 million per year.

The new pharmacovigilance committee structure:

It is considered that the amendments to the EMEA pharmacovigilance committee structure (including replacement of the existing Working Party) would not lead to an increase in costs compared the existing costs.

Revised Community pharmacovigilance referral:

It is considered that the number of referrals is likely to be in the range 10 to 30 per year. If we use the mid point of this range, and assuming the assessment/coordination costs to be equivalent to a Type II variation in the centralised procedure, this will represent a cost to the EMEA in payments to rapporteurs of $20 \times €36,400 = €728,000$ and income from fees of $20 \times €72,800 = €1,46$ million.

Revised transparency and communications provisions:

This is estimated at €646,832 on a yearly basis, covering 4.0 FTEs to manage the documents and the website (including dealing with confidentiality issues and one “communication manager” to formulate urgent safety communications).

¹⁷ Wolters Kluwer Health

One-off information technology costs are also foreseen of €1,000,000 (see section below on impact on overall telematics budget).

Community oversight of non-interventional post-authorisation safety studies

We can estimate the number of protocols to be scrutinised by the EU committee structure as 300 with a cost of €485,124, which comprises 3 FTEs for EMEA coordination and initial screening. Based on the fee estimates above these procedures would attract €1,830,000 in industry fees of which half would be paid to rapporteurs leaving €915,000 to the EMEA.

Community oversight of risk management systems

The number of additional Community assessments of risk management systems is estimated to be 100 per year. Assuming the assessment/coordination costs to be equivalent to a renewal in the centralised procedure, this will represent a cost to the EMEA in payments to rapporteurs of $100 \times €6,050 = €605,000$ and income from fees of $100 \times €12,100 = €1.2$ million.

Enhancements to the Community pharmacovigilance database

Additional one-off development costs for human resources, hardware and software of an estimated €2,871,000 in total (see section below on impact on overall telematics budget).

Running the collection and management of pharmacovigilance data

Additional staff of 10 FTE for running the collection and management of pharmacovigilance data in EudraVigilance from a business perspective (ADR processing) would bear an additional cost estimated at €1.62 million.

PSUR assessment work-sharing:

Based on the fee estimates above these procedures would attract €6,100,000 in industry fees of which half would be paid to rapporteurs leaving €3,050,000 to the EMEA.

Telematics budget

The current EMEA programming for telematics "development costs" (as included in the EMEA Telematics Master Plan) provides for:

Year	2008	2009	2010	2011	2012	2013	Total for period
Pharmacovigilance database costs (€ millions to one decimal place)	1.3	1.4	1.0	1.5	1.7	1.0	8.0
Total IT annual budget (€ millions to one decimal place)	12.6	11.9	13.1	13.1	12.8	10.4	74.1

Based on information provided by the EMEA the transparency and communication provisions in the proposals will incur a one-off information technology cost of €1 Million and Community pharmacovigilance database enhancements will incur a one-off information technology cost of €2.87 Million.

It is reasonable to ask the EMEA to re-programme the one-off €2.87 Million required for the Community pharmacovigilance database from its existing telematics budget (with or without subsidy from any budget surplus for 2008) and to request that the EMEA delivers the

enhanced database functionality prior to the expected entry into force date of 2011. The one – off costs for transparency and communication (€ 1 Million) should be borne by fees (€ 500 000 in 2012 and 2013).

Overall impact on EMEA budget

The calculations estimated a one-off increase of resources for EMEA of €3.9 million (setting up of the EU Safety Portal and enhancement of Eudravigilance functionality) and ongoing costs of €10.1 million annually, including payments to rapporteurs, 23 FTEs needed in addition to the current Agency staff dealing with pharmacovigilance (increase of 38%), and just over €1 million annually for non-staff costs for literature monitoring.

Analysed options (revised if applicable)	EMEA	FTE	EMEA	EMEA	Payments to rapporteurs	Income Fees
	One-off		Salaries annually	Annually	Annually	Annually
Committee + referrals					728,000	1,456,000
Drug safety transparency and communication	1,000,000	4	646,832			
Codification and oversight PASS		3	485,124		915,000	1,830,000
Eudravigilance development	2,871,000*					
Pharmacovigilance data-processing		10	1,617,080			
Literature screening by the EMEA		3	485,124	1,066,667		
PSUR Assessment Worksharing		3	485,124		3,050,000	6,100,000
Risk Management System assessment					605,000	1,210,000
Total	3,871,000	23	3,719,284	1,066,667	5,298,000	10,596,000

*From existing telematics budget (with or without subsidy from any budget surplus for 2008).

Overall impact on EMEA budget by year is predicted in the table below:

EMEA costs	Year 2011	Year 2012	Year 2013	Year 2014	Year 2015	Year 2016
One-off		500,000	500,000			
FTE	5	23	23	23	23	23
Salaries annually	808,540	3,719,284	3,719,284	3,719,284	3,719,284	3,719,284
Other annual costs.		1,066,667	1,066,667	1,066,667	1,066,667	1,066,667
Rapporteurship		5,298,000	5,298,000	5,298,000	5,298,000	5,298,000
Total costs	808,540	10,583,951	10,583,951	10,083,951	10,083,951	10,083,951
Income Fees	0	10,596,000	10,596,000	10,596,000	10,596,000	10,596,000
Balance	-808,540	12,049	12,049	512,049	512,049	512,049

Given the assumptions included in the estimates of work volumes and fee income the net income that appears from 2012 onwards can be regarded as justified to ensure that the key public health function of pharmacovigilance is maintained at the EMEA despite income being variable and some costs (e.g. certain salaries) being fixed. As figures are levelled they have not been index linked.