COMMISSION OF THE EUROPEAN COMMUNITIES

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Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

{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 heath-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 Agency[1], 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 use[2], 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.

1.4. 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

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1 OJ L 136, 30.4.2004, p. 1.
2 OJ L 311, 28.11.2001, p. 67.

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 initiative[3] and the Commission work to stimulate innovation in the pharmaceutical sector, through the 7th Framework programme in general and the Innovative Medicines Initiative[4] 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 events[5].

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. 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.

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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.

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 726/2004[6], 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.

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[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.

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), 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].

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

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.

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amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

(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 Commission[8],

Having regard to the opinion of the European Economic and Social Committee[9],

Acting in accordance with the procedure laid down in Article 251 of the Treaty[10],

Whereas:

(1) Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency[11] creates a Community-wide marketing authorisation procedure (the so-called 'centralised procedure') for certain categories of medicinal products, lays down rules for the pharmacovigilance of those products and establishes the European Medicines Agency (hereinafter referred to as the 'Agency').

(2) Pharmacovigilance rules are necessary for the protection of public health in order to detect, assess and prevent 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.

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8 OJ C , , p. .
9 OJ C , , p. .
10 OJ C , , p. .
11 OJ L 136, 30.4.2004, p. 1.

(4) The main tasks of the Agency in the area of pharmacovigilance laid down in Regulation (EC) No 726/2004 should be maintained and further developed, in particular as regards the management of the Community pharmacovigilance database and data-processing network (hereinafter referred to as 'the Eudravigilance database') and the coordination of safety announcements by the Member States.

(5) In order to allow all competent authorities to receive and access, at the same time, pharmacovigilance information for medicinal products for human use authorised in the Community, and share it, the Eudravigilance database should be maintained and strengthened as the single point of receipt of such information. Member States should therefore not impose on marketing authorisation holders any additional reporting requirements. The database should be fully accessible to the Member States, the Agency and the Commission, and accessible to an appropriate extent to marketing authorisation holders and the public.

(6) In order to increase transparency as regards pharmacovigilance issues, a European medicines safety web-portal should be created and maintained by the Agency.

(7) In order to ensure the availability of the necessary expertise and resources for pharmacovigilance assessments at Community level, it is appropriate to create a new scientific committee within the Agency, the Pharmacovigilance Risk Assessment Advisory Committee. That committee should be composed of independent scientific experts with competence in the safety of medicines including the detection, assessment, minimisation and communication of risk, and the design of post-authorisation safety studies and pharmacovigilance audit.

(8) The rules on scientific committees of the Agency, as laid down in Regulation (EC) No 726/2004, should apply to the Pharmacovigilance Risk Assessment Advisory Committee.

(9) In order to ensure harmonised responses across the Community to safety concerns regarding medicinal products for human use, the Pharmacovigilance Risk Assessment Advisory Committee should support the Committee for Medicinal Products for Human Use and the coordination group established by Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use[12] on any question relating to the pharmacovigilance of medicinal products for human use. However, for the sake of consistency and continuity of the assessments, the final responsibility for the risk-benefit assessment of medicinal products for human use authorised in accordance with this Regulation should remain with the Committee for Medicinal Products for Human Use of the Agency and with the authorities competent for the granting of marketing authorisations.

(10) In accordance with Directive 2001/83/EC the Agency provides the secretariat to the coordination group . In view of the enlarged mandate of the coordination group in the area of pharmacovigilance, the technical and administrative support by the secretariat of the Agency to the coordination group should be reinforced. Provision should be made for the Agency to ensure appropriate coordination between the coordination group and the Agency's scientific committees.

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[12] OJ L 311, 28.11.2001, p. 67.

(11) In order to protect public health, there should be adequate funding of activities related to pharmacovigilance by the Agency. Provision should be made to allow adequate funding for pharmacovigilance activities through the collection of fees charged to marketing authorisation holders. The management of those collected funds should be under a permanent control of the Management Board in order to guarantee the independence of the Agency.

(12) To ensure the highest levels of expertise and the functioning of the Pharmacovigilance Risk Assessment Advisory Committee, rapporteurs providing assessment for Community pharmacovigilance procedures, periodic safety update reports, post-authorisation safety study protocols and risk management systems should receive payment through the Agency.

(13) Provision should be made for the Agency to collect fees as regards the activities of the coordination group within the Community system of pharmacovigilance, as provided for in Directive 2001/83/EC, and for rapporteurs within the coordination group to be then paid by the Agency.

(14) In order to ensure the collection of any necessary additional data about the safety of medicinal products authorised in accordance with Regulation (EC) No 726/2004, the Commission should be empowered to require the marketing authorisation holder to conduct post-authorisation safety studies at the time of the granting of the marketing authorisation or later, and that requirement should be included as a condition of the marketing authorisation.

(15) Where a medicinal product is authorized subject to the requirement to conduct a post-authorisation safety study or subject to 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 kept up to date by the Agency.

(16) Experience has shown that there is a need to clarify the responsibilities of marketing authorisation holders for the pharmacovigilance of authorised products. The marketing authorisation holder should be responsible for continuously monitoring the safety of his products, for informing the authorities of any changes that might have an impact on the marketing authorisation, and for ensuring that the product information is kept 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 all relevant information collected on the safety of the medicinal product is taken into account when marketing authorisations are being renewed.

(17) Scientific and medical literature provides an important source of information on suspected adverse reaction case reports. Currently, for active substances included in more than one medicinal product, literature cases are reported in a duplicative way. In order to enhance the efficiency of reporting, provision should be made for the Agency

to monitor a defined list of literature for a defined list of active substances used in medicinal products for which there are several marketing authorisations.

(18) As a result of the submission of all adverse reaction data for medicinal products authorised by the Member States directly to the Eudravigilance database, it is not necessary to provide for different reporting rules for medicinal products for human use authorised in accordance with Regulation (EC) No 726/2004. The rules on adverse reaction recording and reporting laid down in Directive 2001/83/EC should therefore apply to medicinal products for human use authorised in accordance with Regulation (EC) No 726/2004.

(19) There is a need to increase the shared use of resources between competent authorities for the assessment of periodic safety update reports. The procedures of Directive 2001/83/EC should therefore apply for the single assessment of periodic safety update reports for different medicinal products containing the same active substance or combination thereof, including joint assessments of products authorised nationally and through the centralised procedure.

(20) It is appropriate to strengthen the supervisory role for medicinal products authorised through the centralised procedure by providing that the supervisory authority for pharmacovigilance should be the competent authority of the Member State in which the pharmacovigilance system master file of the marketing authorisation holder is sited.

(21) The provisions on the surveillance of medicinal products for human use in Regulation (EC) No 726/2004 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 339/93[13].

(22) Regulation (EC) No 726/2004 should therefore be amended accordingly,

HAVE ADOPTED THIS REGULATION:

Article 1
Amendments to Regulation (EC) No 726/2004

Regulation (EC) No 726/2004 is amended as follows:

(1) In Article 5(2) the following sentence is added:

"For the fulfilment of its pharmacovigilance tasks, it shall be assisted by the Pharmacovigilance Risk Assessment Advisory Committee referred to in Article 56(1)(aa)."

[13] OJ L 218, 13.8.2008, p. 30.

(2) Article 9(4) is amended as follows:

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

“(aa) a recommendation on the frequency of submission of periodic safety update reports;”

(b) the following points (ca) and (cb) are inserted:

“(ca) details of any measures for the safe use of the medicinal product contained in the risk management system to be imposed as conditions of the marketing authorisation;

(cb) if appropriate, the written requirement to conduct post-authorisation safety studies or to comply with requirements on adverse reaction recording or reporting which are stricter than those referred to in Chapter 3;”

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

“(f) the assessment report 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.”

(3) Article10 is amended as follows:

(a) Paragraph 1 is replaced by the following`:

"1. Within 15 days after receipt of the opinion referred to in Article 5(2), the Commission shall prepare a draft of the decision to be taken in respect of the application.

Where a draft decision envisages the granting of a marketing authorisation, it shall include or make reference to the documents mentioned in points (a) to (d) of Article 9(4).

Where a draft decision envisages the granting of a marketing authorisation subject to the conditions referred to in points (c), (ca) or (cb) of Article 9(4), it shall lay down deadlines for the fulfilment of the conditions where necessary.

Where the draft decision is not in accordance with the opinion of the Agency, the Commission shall annex a detailed explanation of the reasons for the differences.

The draft decision shall be forwarded to Member States and the applicant."

(b) Paragraph 6 is replaced by the following:

“6. The Agency shall disseminate the documents referred to in points (a) to (d) of Article 9(4), together with any deadlines laid down pursuant to the third subparagraph of paragraph 1 of this Article.”

(4) The following Article 10a is inserted:

"Article 10a

1. After the granting of a marketing authorisation, the Agency 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 Agency 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 Commission shall withdraw or confirm the requirement. Where the Commission 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."

(5) Article 14 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 Agency 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 Chapter 3, 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 Commission decides, on justified grounds relating to pharmacovigilance or insufficient exposure to the product, to proceed with one additional five-year renewal in accordance with paragraph 2."

(c) Paragraph 8 is replaced by the following:

"8. 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 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 to Directive 2001/83/EC. Continuation of the authorisation shall be linked to the annual reassessment of these conditions."

(6) The following Article 14a is inserted:

"Article 14a

1. The marketing authorisation holder shall incorporate any conditions or requirements referred to in points (c), (ca) and (cb) of Article 9(4) or in Articles 10a, 14(7) and (8) in his risk management system.

2. The Agency shall include the medicinal products concerned by paragraph 1 in the list referred to in Article 23. The Agency shall remove a medicinal product from the list when the Commission, on the basis of an opinion of the Agency, concludes that the conditions 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.

(7) Article 16 is replaced by the following:

"Article 16

1. After an authorisation has been granted in accordance with this Regulation, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h) of Directive 2001/83/EC, take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods. He shall apply for approval of such variations in accordance with this Regulation.

2. The marketing authorisation holder shall forthwith supply to the Agency, to the Commission and to the member States 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) of Directive 2001/83/EC, in Annex I thereto, or in Article 9(4) of this Regulation.

In particular, he shall forthwith inform the Agency and the Commission 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.

4. In order that the risk-benefit balance may be continuously assessed, the Agency may at any time ask the holder of the marketing authorisation to forward data demonstrating that the risk-benefit balance remains favourable.

The Agency 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."

(8) Article 18 is amended as follows:

(a) Paragraph 1 is replaced by the following:

"1. In the case of medicinal products for human use manufactured within the Community, the supervisory authorities for manufacturing shall be the competent authorities of the Member State or Member States which granted the manufacturing authorisation provided for in Article 40(1) of Directive 2001/83/EC in respect of the medicinal product concerned."

(b) In paragraph 2, the first subparagraph is replaced by the following:

"In the case of medicinal products imported from third countries, the supervisory authorities for imports shall be the competent authorities of the Member State or Member States that granted the authorisation provided for in Article 40(3) of Directive 2001/83/EC to the importer, unless appropriate agreements have been made between the Community and the exporting country to ensure that those controls are carried out in the exporting country and that the manufacturer applies standards of good manufacturing practice at least equivalent to those laid down by the Community."

(c) The following paragraph 3 is added:

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

(9) Article 19 is amended as follows:

(a) Paragraph 1 is replaced by the following:

"1. Under the coordination of the Agency, the supervisory authorities for manufacturing and imports shall be responsible for verifying on behalf of the Community that the holder of the marketing authorisation for the medicinal product for human use or the manufacturer or importer established within the Community satisfies the requirements concerning manufacturing and imports laid down in Titles IV and XI of Directive 2001/83/EC.

Under the coordination of the Agency, the supervisory authorities for pharmacovigilance shall be responsible for verifying on behalf of the Community that the holder of the marketing authorisation for the medicinal product for human use satisfies the pharmacovigilance requirements laid down in Titles IX and XI of Directive 2001/83/EC."

(b) In paragraph 3, the second subparagraph is replaced by the following:

“The inspection shall be undertaken by inspectors from the Member States who possess the appropriate qualifications; they may be accompanied by a rapporteur or expert appointed by the said Committee. The report of the inspectors shall be made available electronically to the Commission, the Member States and the Agency."

(10) Article 20 is amended as follows:

(a) Paragraph 3 is replaced by the following:

“3. Following an opinion by the Agency, the Commission may adopt the necessary provisional measures, which shall be applied immediately.

A final decision in respect of the medicinal product concerned shall be adopted within six months, in accordance with the procedure referred to in Article 87(2).

The Commission may also adopt a decision addressed to the Member States pursuant toArticle 127a of Directive 2001/83/EC.”

(b) The following paragraph 8 is added:

“8. By way of derogation from paragraphs 1 to 7 of this Article, where a procedure under Articles 31, 36 or 107i to 107l of Directive 2001/83/EC concerns a range of medicinal products or a therapeutic class, medicinal products authorised in accordance with this Regulation and which belong to that range or class shall only be included in the procedure of Article 31, 36 or of Articles 107i to 107l of the Directive.

(11) Chapter 3 of Title II is replaced by the following:

“Chapter 3
Pharmacovigilance

Article 21

1. The obligations of marketing authorisation holders laid down in Article 104 of Directive 2001/83/EC shall apply to marketing authorisation holders for medicinal products for human use authorised in accordance with this Regulation.

However, holders of marketing authorisations granted before [insert concrete date - date set out in the second paragraph of Article 3 of Regulation (EC) No …/…] shall operate a risk management system as referred to in point (c) of Article 104(3) of that Directive only if paragraphs 2, 3 and 4 of this Article are complied with.

2. The Agency may require a marketing authorisation holder to operate a risk management system as referred to in point (c) of Article 104(3) of Directive 2001/83/EC, if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. To this effect, the Agency 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 Agency 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 Commission shall withdraw or confirm the requirement. Where the Commission confirms the requirement, the marketing authorisation shall be varied as appropriate to include measures to be taken in the risk management system as conditions of the marketing authorisation as referred to in point (ca) of Article 9(4).

Article 22

The obligations of marketing authorisation holders laid down in Article 106a(1) of Directive 2001/83/EC, and of the Member States, the Agency and the Commission laid down in paragraphs (2), (3) and (4) of that Article shall apply to safety announcements concerning medicinal products for human use authorised in accordance with this Regulation.

Article 23

The Agency shall establish and make public a list of medicinal products for human use under intensive monitoring.

That list shall include the names and active substances of medicinal products authorised pursuant to this Regulation subject to conditions or requirements referred to in points (c), (ca) and (cb) of Article 9(4), or in Articles 10a, 14(7) and 14(8), and of medicinal products authorised pursuant to Directive 2001/83/EC which are referred to in Articles 21a, 22 and 22a thereof, and an electronic link to the product information.

The Agency shall keep the list up to date.

Article 24

1. The Agency, in collaboration with the Member States and the Commission, shall set up and maintain a database and data processing network (hereinafter ‘the Eudravigilance database’) to collate pharmacovigilance information regarding medicinal products authorised in the Community and to allow competent authorities to access the information at the same time and to share it.

The Eudravigilance database shall contain information on 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. The Eudravigilance database shall be fully accessible to the competent authorities of the Member States and to the Agency and the Commission. It shall also be accessible to

marketing authorisation holders to the extent necessary for them to comply with their pharmacovigilance obligations.

The Agency shall ensure that health-care professionals and the public have appropriate levels of access to the Eudravigilance database, with personal data protection being guaranteed.

The data held on the Eudravigilance database shall be made publicly accessible in an aggregated format together with an explanation of how to interpret the data.

3. Individual adverse reaction reports held on the Eudravigilance database may be requested by the public. Those reports shall be provided by the Agency or the national competent authority from which they are requested within 90 days, unless disclosure would compromise the anonymity of the subjects of the reports.

Article 25

The Agency, in collaboration with the Member States, shall develop standard web-based structured forms for the reporting of suspected adverse reactions by health-care professionals and patients.

Article 26

The Agency, in collaboration with the Member States and the Commission, shall set up and maintain a European medicines safety web-portal for the dissemination of information on pharmacovigilance of medicinal products authorised in the Community. By means of that portal, the Agency shall make public at least the following:

(1) the members of the committees referred to in points (a) and (aa) of Article 56(1) of this Regulation and the members of the coordination group referred to in Article 27 of Directive 2001/83/EC (hereinafter 'the coordination group'), together with their professional qualifications and with the declarations pursuant to Article 63(2) of this Regulation;

(2) a summary of each meeting of the committees referred to in points (a) and (aa) of Article 56(1) of this Regulation and the coordination group as regards pharmacovigilance activities;

(3) risk management systems for medicinal products authorised in accordance with this Regulation;

(4) the list of medicinal products under intensive monitoring referred to in Article 23 of this Regulation;

(5) a list of the locations in the Community where pharmacovigilance system master files are sited and contact information for pharmacovigilance enquiries, for all medicinal products authorised in the Community;

(6) information about how to report suspected adverse reactions to medicinal products and standard forms for their web-based reporting by patients and health-care professionals;

(7) Community reference dates and frequency of submission of periodic safety update reports established in accordance with Article 107c of Directive 2001/83/EC;

(8) protocols and public abstracts of results as regards post authorisation safety studies conducted in more than one Member State and referred to in Articles 107o and 107q of Directive 2001/83/EC;

(9) the initiation of the procedure under Articles 107i to 107l of Directive 2001/83/EC, the substances or products concerned and the issue being addressed, any public hearings pursuant to that procedure and information on how to submit information and to participate in public hearings;

(10) Assessment conclusions, recommendations, opinions and decisions taken by the committees referred to in points (a) and (aa) of Article 56(1) of this Regulation and the coordination group, the national competent authorities and the Commission in the framework of the procedures of Articles 28, 28a and 28b of this Regulation and of sections 2 and 3 of Chapter 3 of Title IX of Directive 2001/83/EC.

Article 27

1. The Agency shall monitor selected medical literature for reports of suspected adverse reactions to medicinal products for human use containing certain active substances. It shall publish the list of active substances being monitored and the publications subject to this monitoring.

2. The Agency shall enter into the Eudravigilance database relevant information from the selected literature.

3. The Agency shall, in consultation with the Commission, Member States and interested parties, draw up a detailed guide regarding the conduct of medical literature monitoring and the entry of relevant information into the Eudravigilance database.

Article 28

1. The obligations of marketing authorisation holders and of Member States laid down in Articles 107 and 107a of Directive 2001/83/EC shall apply to the recording and reporting of suspected adverse reactions for medicinal products for human use authorised in accordance with this Regulation.

2. The obligations of marketing authorisation holders laid down in Article 107b of Directive 2001/83/EC and the procedures under Article 107b and Article 107c thereof shall apply to the submission of periodic safety update reports, the establishment of Community reference dates and changes to the frequency of submission of periodic safety update reports for medicinal products for human use authorised in accordance with this Regulation.

The rules for the submission of periodic safety update reports laid down in the second subparagraph of Article 107c(2) of that Directive shall apply to holders of marketing authorisations which were granted before [insert concrete date - date set out in the second paragraph of Article 3 of Regulation (EC) No …/…] and for which the frequency and dates of submission of the periodic safety update reports are not laid down as a condition to the

marketing authorisation until another frequency or other dates of submission of the reports are laid down in the marketing authorisation or determined in accordance with Article 107c of that Directive.

3. The Pharmacovigilance Risk Assessment Advisory Committee shall assess the periodic safety update reports.

It shall prepare an assessment report within 90 days of receipt of the periodic safety update report and send it to the marketing authorisation holder.

Within 30 days of receipt of the assessment report, the marketing authorisation holder may submit comments to the Agency.

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

4. Within 30 days of receipt of the report by the Pharmacovigilance Risk Assessment Advisory Committee, the Committee for Medicinal Products for Human Use shall consider the report and adopt an opinion on the maintenance, variation, suspension or revocation of the marketing authorisation concerned.

Where the opinion states that regulatory action is necessary, the Commission shall adopt a decision to vary, suspend or revoke the marketing authorisation. Article 10 of this Regulation shall apply to the adoption of that decision. Where the Commission adopts such decision, it may also adopt a decision addressed to the Member States pursuant to Article 127a of Directive 2001/83/EC.

5. In the case of an assessment of periodic safety update reports concerning more than one marketing authorisation in accordance with Article 107e(1) of Directive 2001/83/EC which includes at least one marketing authorisation granted in accordance with this Regulation, the procedure laid down in Articles 107e and 107g of that Directive shall apply.

6. The opinions and decisions referred to in paragraphs 3 to 5 of this Article shall be made public by means of the European medicines safety web-portal referred to in Article 26.

Article 28a

1. Regarding medicinal products authorised in accordance with this Regulation, the Agency and marketing authorisation holders 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 points (c), (ca) and (cb) of Article 9(4) or in Articles 10a, 14(7) and (8) ;

(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.

2. The Pharmacovigilance Risk Assessment Advisory Committee shall perform the initial scrutiny and prioritisation of indications of new or changed 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 Article 28.

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

Article 28b

1. For post-authorisation safety studies concerning medicinal products for human use authorised in accordance with this Regulation which fulfil the criteria set out in Article 107n(1) of Directive 2001/83/EC, Articles 107n(2), 107o to 107q and Article 107r (1) thereof shall apply.

2. Where, in accordance with the procedure referred to in paragraph 1 of this Article, the Pharmacovigilance Risk Assessment Advisory Committee makes recommendations for the variation, suspension or revocation of the marketing authorisation, the Committee on Medicinal Products for Human Use shall adopt an opinion taking into account the recommendation and the Commission shall adopt a decision in accordance with Article 10.

Article 28c

1. The Agency shall collaborate with the World Health Organisation in matters of pharmacovigilance and shall take the necessary steps to submit to it, promptly, appropriate and adequate information regarding the measures taken in the Community which may have a bearing on public health protection in third countries.

The Agency shall make available all suspected adverse reaction reports that occurred in the Community to the World Health Organization.

2. Information received on abuse of medicinal products including information related to illicit drugs shall be exchanged between the Agency and the European Monitoring Centre for Drugs and Drug Addiction.

Article 28d

Upon request of the Commission, the Agency shall participate in collaboration with the Member States in international harmonization and standardization of technical measures in pharmacovigilance.

Article 28e

The Agency and the Member States shall cooperate to continuously develop pharmacovigilance systems capable of achieving high standards of public health protection for all medicinal products, regardless of routes of authorisation, including the use of collaborative approaches, to maximise use of resources available within the Community.

Article 28f

The Agency shall perform regular audit of its pharmacovigilance tasks and report the results to its Management Board on a two-yearly basis.

Article 29

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

Those measures, designed to amend non-essential elements of this Regulation, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).

Article 29a

The Commission shall make public a report on the conduct of pharmacovigilance tasks by the Agency on [insert concrete date - three-years after the date of application set out in the second paragraph of Article 3] at the latest and then every three years thereafter."

(12) Article 56(1) is amended as follows:

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

"(aa) the Pharmacovigilance Risk Assessment Advisory Committee, which shall be responsible for providing advice to the Committee for Medicinal Products for Human Use and the coordination group on any question relating to the pharmacovigilance of medicinal products for human use;"

(b) point (f) is replaced by the following:

"(f) a Secretariat, which shall provide technical, scientific and administrative support for the committees and ensure appropriate coordination between them, and which shall provide technical and administrative support for the coordination group and ensure appropriate coordination between it and the committees."

(13) Article 57 is amended as follows:

(a) in paragraph 1, points (c) to (f) are replaced by the following:

"(c) coordination of the supervision of medicinal products which have been authorised within the Community and the provision of advice on the measures necessary to ensure the safe and effective use of these products, in particular by coordinating the evaluation and

implementation of pharmacovigilance obligations and systems and the monitoring of such implementation;

(d) ensuring the collation and dissemination of information on adverse reactions to medicinal products authorised in the Community by means of a database permanently accessible to all Member States;

(e) assisting Member States with the rapid communication of information concerning pharmacovigilance to health-care professionals and coordinating the safety announcements of the national competent authorities;

(f) distributing appropriate pharmacovigilance information to the general public, in particular by setting up and maintaining a European medicines safety web-portal;"

(b) In paragraph 2, the following subparagraph is inserted after the first subparagraph:

"For the purposes of the database, the Agency shall establish a list of all medicinal products authorised in the Community. To this effect the following measures shall be taken:

(a) the Agency shall, by -/- (*insert date - six-months after the entry into force of the amending regulation*) at the latest, make public a format for the electronic submission of medicinal product information;

(b) marketing authorisation holders shall, by -/- (*insert date - eighteen months after the entry into force of the amending regulation*) at the latest, electronically submit to the Agency information for all medicinal products authorised or registered in the Community, using the format referred to in point (a);

(c) from the date set out in point (b), marketing authorisation holders shall inform the Agency of any new authorisations granted in the Community, using the format referred to in point (a)."

(14) The following Article 61a is inserted:

"Article 61a

1. The Pharmacovigilance Risk Assessment Advisory Committee shall be composed of the following:

(a) ten members and ten alternates appointed by the Management Board, on the basis of proposals by the national competent authorities;

(b) five members and five alternates appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament.

The alternates shall represent and vote for the members in their absence.

The Commission may adapt the number of members and alternates in the light of technical and scientific needs. Those measures, designed to amend non-essential elements of this

Regulation, shall be adopted in accordance with the regulatory procedure with scrutiny referred to in Article 87(2a).

2. The members and alternates of the Pharmacovigilance Risk Assessment Advisory Committee shall be appointed on the basis of their relevant expertise in pharmacovigilance and risk assessment of medicinal products for human use, in such a way as to guarantee the highest levels of specialist qualifications and a broad spectrum of relevant expertise. For this purpose, the Executive Director of the Agency shall assist the Management Board and the Commission in order to ensure that the final composition of the Committee covers the scientific areas relevant to its tasks.

3. The members and alternates of the Pharmacovigilance Risk Assessment Advisory Committee shall be appointed for a term of three years, which may be prolonged once. The Committee shall elect its Chairman among its members for a term of three years, which may be prolonged once.

4. Paragraphs (3), (4), (7) and (8) of Article 61 shall apply to the Pharmacovigilance Risk Assessment Advisory Committee.

5. Members and alternates of the Pharmacovigilance Risk Assessment Advisory Committee may not seek or take instructions from any national competent authority, organisation or person. They shall carry out the duties assigned to them objectively and impartially.

6. Representatives of the national competent authorities shall be entitled to attend all meetings of the Pharmacovigilance Risk Assessment Advisory Committee to facilitate appropriate coordination between the tasks of the Agency and the work of national competent authorities. They may provide clarification or information if invited to do so but shall not seek to influence discussions."

(15) Article 62 is amended as follows:

(a) Paragraph 1 is amended as follows:

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

"Where, in accordance with this Regulation, any of the committees referred to in Article 56(1) is required to evaluate a medicinal product, it shall appoint one of its members to act as rapporteur for the coordination of the evaluation. The Committee concerned may appoint a second member to act as co-rapporteur."

(ii) the fourth subparagraph is replaced by the following:

"If there is a request for re-examination of one of its opinions where this possibility is foreseen in the Community legislation, the Committee concerned shall appoint a different rapporteur and, where necessary, a different co-rapporteur from those appointed for the initial opinion. The re-examination procedure may deal only with the points of the opinion initially identified by the applicant and may be based only on the scientific data available when the Committee adopted the initial opinion. The applicant may request that the Committee consults a scientific advisory group in connection with the re-examination."

(b) in paragraph 2, the first subparagraph is replaced by the following:

" Member States shall transmit to the Agency the names of national experts with proven experience in the evaluation of medicinal products who would be available to serve on working parties or scientific advisory groups of any of the committees referred to in Article 56(1), together with an indication of their qualifications and specific areas of expertise."

(c) In paragraph 3, the following subparagraph is added:

"The first and second subparagraph shall apply also to the work of rapporteurs in the coordination group as regards the fulfilment of its tasks in accordance with Articles 107c, 107e, 107g, 107l and 107r of Directive 2001/83/EC."

(16) Article 64(2) is amended as follows:

(a) Point (b) is replaced by the following:

"(b) for managing all the Agency resources necessary for conducting the activities of the committees referred to in Article 56(1), including making available appropriate scientific and technical support to those committees, and for making available appropriate technical support to the coordination group;"

(b) Point (d) is replaced by the following:

"(d) for ensuring appropriate coordination between the committees referred to in Article 56(1) and, where necessary, between the committees and the coordination group;"

(17) In Article 66(g), the figure "67" is replaced by the figure "68".

(18) Article 67 is amended as follows:

(a) In paragraph 3, the first subparagraph is replaced by the following:

"The Agency's revenue shall consist of a contribution from the Community and fees paid by undertakings for obtaining and maintaining Community marketing authorisations and for other services provided by the Agency or the coordination group as regards the fulfilment of its tasks in accordance with in accordance with Articles 107c, 107e, 107g, 107l and 107r of Directive 2001/83/EC."

(b) Paragraph 4 is replaced by the following:

"4. Activities relating to pharmacovigilance, to the operation of communications networks and to market surveillance shall be under the permanent control of the Management Board in order to guarantee the independence of the Agency. This shall not preclude the collection of fees to be paid by marketing authorisation holders for the carrying out of these activities by the Agency."

(19) Article 82(3) is replaced by the following:

"3. Without prejudice to the unique, Community nature of the content of the documents referred to in points (a) to (d) of Article 9(4) and in points (a) to (e) of Article 34(4), this

Regulation shall not prohibit the use of two or more commercial designs for a given medicinal product covered by a single authorisation."

(20) In Article 83(6), the second sentence is replaced by the following:

"Article 28(1) and (2) shall apply *mutatis mutandis*."

Article 2
Transitional provisions

1. 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 Directive …/…/EC, which applies to medicinal products authorised pursuant to Regulation (EC) No 726/2004 by virtue of its Article 9(4)(a) and (d), shall apply to a marketing authorisation granted before the date set out in the second paragraph of Article 3 of this Regulation from renewal of that authorisation or from the expiry of a period of three years starting from that date, whichever is the earliest.

2. 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 Directive …/…/EC, which applies to medicinal products authorised pursuant to Regulation (EC) No 726/2004 by virtue of Article 21 of Regulation (EC) No 726/2004 as amended by this Regulation, shall apply to marketing authorisations granted before the date set out in the second paragraph of Article 3 of this Regulation or from the expiry of a period of three years starting from that date.

3. The procedure under Articles 107n to 107r of Directive 2001/83/EC as amended by Directive …/…/EC, which apply by virtue of Article 28b of Regulation (EC) No 726/2004 as amended by this Regulation, shall apply only to studies which have commenced after the date set out in the second paragraph of Article 3 of this Regulation.

Article 3
Entry into force and application

This Regulation shall enter into force on day following that of its publication in the Official Journal of the European Union.

It shall apply from [18 months from the entry into force].

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[14]	NO	YES	NO	**No** 1a0203
02.030202	Non-comp	Non-diff	NO	YES	NO	**No** 1a0203

[14] Non-differentiated appropriations hereafter referred to as NDA.

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 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"[15], 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.

[15] 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 –EMEA. 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 EMEA in London has been provided by the EMEA (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 EMEA and 50% paid to rapporteurs.

Fees charged by the EMEA 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 EMEA 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 company[16] (€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 x €36,400 = €728,000 and income from fees of 20 x €72,800 = €1,46 million.

[16] Wolters Kluwer Health.

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).

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 x €6,050 = €605,000 and income from fees of 100 x €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.