



Brussels, 5 December 2007

***STRATEGY TO BETTER PROTECT PUBLIC HEALTH BY STRENGTHENING AND
RATIONALISING EU PHARMACOVIGILANCE:***

PUBLIC CONSULTATION ON LEGISLATIVE PROPOSALS

Section 1 Introduction to the consultation

DG Enterprise and Industry wishes to consult stakeholders on legislative proposals to strengthen and rationalise the EU system of pharmacovigilance.

The Commission services conducted a previous consultation, between 16 March 2006 and 12 May 2006, which sought stakeholders' views on the strengths and weaknesses of the current EU system of pharmacovigilance and how the system could be strengthened. The web-based consultation was supplemented by public workshops in April 2006, as well as, meetings with specific stakeholder groups. The consultation results were made public in February 2007 and at the same time, in response to the consultation outcome, Vice-President Verheugen announced its "*Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance*". The Strategy has two parts: 1. better implementation of the current framework and, 2. proposals for change to the legal framework. Details of both the 2006 consultation and the Strategy are available on the Commission's website¹.

This public consultation specifically addresses part 2 of the strategy, the proposals for changes to the legal framework. This consultation paper is organised in the following sections:

- Ø Section 1 introduces the consultation, explains how and by when to submit consultation responses and explains the next steps.
- Ø Section 2 provides a brief orientation on pharmacovigilance and the background to the strategy.
- Ø Section 3 presents the legislative strategy and the key proposals for legislative change.
- Ø Section 4 presents detailed proposals to change EU legal texts.

The public consultation is open from 4 December 2007 to 1 February 2008. Stakeholders may wish to comment on the key proposals presented in Section 3 or may prefer to comment on the detailed proposals to change EU legal texts presented in Section 4. All

¹ For the consultation results and the Commission strategy see:
http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/index.htm

comments should be sent electronically to Dr Peter Arlett (peter.arlett@ec.europa.eu) by 1 February 2008.

All submissions received by this date will be acknowledged and will be carefully assessed and taken into consideration before the Commission adopts proposals to the European Parliament and Council which are scheduled for 2008. Stakeholders will wish to note that consultation responses will be made public and feedback on the consultation will be included in the Impact Assessment and the Explanatory Memorandum that will accompany the legislative proposals.

Section 2: Pharmacovigilance and background to the strategy

Pharmacovigilance is the process and science of monitoring the safety of medicines and taking action to reduce risks and increase benefits from medicines. It is a key public health function and comprises:

- Collecting and managing data on the safety of medicines
- Looking at the data to detect ‘signals’ (any new or changing safety issue)
- Evaluating the data and making decisions with regard to safety issues
- Acting to protect public health (including regulatory action)
- Communicating with stakeholders
- Audit, both of the outcomes of action taken and of the key processes involved.

Those directly involved in pharmacovigilance include:

- Patients as the users of medicines
- Doctors, pharmacists, nurses and all other healthcare professionals working with medicines
- Regulatory authorities including the European Medicines Agency and those in each Member State responsible for monitoring the safety of medicines
- Pharmaceutical companies, and companies importing or distributing medicines.

Pharmacovigilance rules in the EU are included in the Community Code on medicinal products for human use (Directive 2001/83/EC as amended), in a regulation of the European Parliament and the Council for centrally authorised products (Regulation (EC) No 726/2004), in a Commission Regulation (Regulation (EC) No 540/95) and in Commission guidance (Volume 9A of Eudralex²). Although the legislation was updated in 2004 (the so-called “2001 Review”) the changes to the pharmacovigilance provisions were relatively minor. Importantly there was no thorough review of the pharmacovigilance provisions and as a result the current provisions have become gradually more complex over time and do not reflect the evolution in science and technology that has occurred, including the opportunities for simplification offered by the full use of modern information technology.

While fully recognising that medicines can save lives and relieve suffering, there is abundant evidence of the public health burden that adverse reactions to medicines cause with adverse reactions to medicines being a common cause of death. It follows from an

² For Eudralex see: <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm>

independent study³ and the 2006 public consultation that the EU system of pharmacovigilance places significant administrative burdens on industry and competent authorities while weaknesses in the system continue. The current EU legal framework is complex and duplicative and there are a lack of clear roles and responsibilities. A lack of harmonisation of pharmacovigilance requirements among the Member States has led to complex and diverse reporting requirements for the industry and this clearly interferes with the functioning of the single market for medicinal products. Furthermore, a lack of fast and coherent EU action in response to drug safety alerts may put patient safety at risk. Stakeholders are calling for the EU system to be rationalised and strengthened.

Section 3 Legislative strategy and the key proposals for legislative change

Section 3.1 Legislative strategy

To strengthen and rationalise the EU pharmacovigilance system requires:

- Ø changes to Directive 2001/83/EC,
- Ø changes to Regulation (EC) No 726/2004, and,
- Ø annulment of Regulation (EC) No 540/95.

Because Directive 2001/83/EC and Regulation (EC) No 726/2004 are co-decision acts (i.e. they are legal acts adopted by the European Parliament and the Council of Ministers) their amendment in turn requires co-decision acts. Furthermore, as the changes required to ensure a robust EU pharmacovigilance system impact on different sections of the existing legislation the only way to realise these amendments is by:

- Ø a directive of the European Parliament and the Council amending Directive 2001/83/EC and annulling Regulation (EC) No 540/95, and,
- Ø a regulation of the European Parliament and the Council amending Regulation (EC) No 726/2004,

The Commission work programme foresees adoption of proposals for a directive and a regulation of the European Parliament and the Council during the 4th quarter of 2008.

Section 3.2 Key proposals for legislative change

3.2.1. Fast robust EU decision-making on safety issues by rationalising the existing EU referral procedures and reinforcing the committee structure

Key changes to EU legislation

Within the European Medicines Agency (EMA), establish a committee (to replace the existing Pharmacovigilance Working Party) with clear responsibility for coordinating pharmacovigilance and for making recommendations on the safety of medicines to the existing Committee on Human Medicinal Products.

Rationalise the referral procedures for nationally authorised products: to ensure subsidiarity but also effectiveness have clear obligatory triggers (important safety concerns, including withdrawal of products, restrictions to indications and new

³ Both the study report is an annex to the 2006 consultation document and can be found at :
http://ec.europa.eu/enterprise/pharmaceuticals/pharmacovigilance_acs/docs/acs_consultation_final.pdf

contraindications); referrals to have light procedures and public hearings; the output of referrals will be binding Commission decisions to ensure that for important safety issues safety action is taken in all Member States to protect the health of European patients.

Why

Current legal provisions on referrals are unclear and overlapping and the use of the provisions is limited. Instead the existing 'Pharmacovigilance Working Party' at the EMEA informally discusses important safety issues but its conclusions are frequently not implemented and certainly not implemented comprehensively across all Member States (as they are not legally binding on the Member States or companies). This leads to divergent safety action by the Member States which represents a weakness of public health protection, creates obstacles for the single market and is costly for the industry.

Impact

Adverse reactions to medicines are the 5th most common cause of death in hospital and there is abundant evidence of the major public health burden that adverse drug reactions cause. There will be a major benefit to public health by ensuring that important safety issues are rapidly and robustly dealt with across the EU.

There will be cost savings for industry and national regulators as safety issues will be dealt with in one coordinated, fast and robust EU procedure rather than disparate national reviews, studies and actions. There will be increase in costs to the EMEA due to the replacement of the old working party with a formal Committee with clearly defined tasks.

There is an established link between pharmacovigilance and innovation, whereby investor confidence in funding pharmaceutical R&D is linked to the robustness of pharmacovigilance, and regulatory authority decision-making when authorising products is directly linked to the robustness of post-authorisation pharmacovigilance. This means that products can be authorised earlier in their development and this is of crucial benefit to patients with unmet medical needs. In addition, earlier product authorisation provides faster return on investment and, by reducing the cost of capital the total cost of product development is reduced.

3.2.2. Clarify / codify roles and responsibilities and codify standards for industry and regulators

Key changes to EU legislation

For the Member State competent authorities, EMEA (including its committees), Commission and Marketing Authorisation holders including their qualified person, clarify and codify the tasks and responsibilities in the legislation.

To support inspections and quality management, establish the concept and scope of Good Vigilance Practices (GVP) in co-decision texts and create the legal basis for the Commission to adopt a regulation on 'GVP' via comitology.

Why

Currently the roles, responsibilities and standards are overlapping and unclear leading to poor compliance, a lack of legal certainty, and this does not facilitate public health protection.

Impact

Benefit to public health by ensuring that the parties know what is expected of them and by supporting inspection and audit (and thus quality management). Stimulation of innovation will help fulfil unmet medical needs.

Clear roles and responsibilities will increase the robustness of pharmacovigilance which will drive innovation by increasing confidence and reducing costs and also supports earlier access of new medicines to fulfil patients' unmet medical needs.

Industry and national regulators administrative costs will not change in the long-term (due to minimising duplication of effort and conduct of unnecessary tasks).

3.2.3. Simplify informing the authorities about the company pharmacovigilance system

Key changes to EU legislation

Simplify the existing requirement for a 'detailed description of the pharmacovigilance system' to be submitted and kept up to date. At marketing authorisation only key elements of the pharmacovigilance system to be submitted as part of the dossier.

To compensate for reduction in regulatory scrutiny companies will maintain on site a detailed file on their Pharmacovigilance System ("Pharmacovigilance System Master File") and this will be submitted on request by the authorities or can be viewed during inspections. Linked to this there will be a clarification of the legal basis for pharmacovigilance inspections.

For centrally authorised products create a specific supervisory authority for pharmacovigilance which is the Member State where the company Qualified Person resides.

Why

The requirement to submit with the market authorisation a "detailed description of the pharmacovigilance system" is a major administrative burden at present for industry and regulators because any change to a company system has to be via a variation to the marketing authorisation (for each product and each national authority). If the current law is complied with a minor change in a companies pharmacovigilance system could necessitate hundreds of variations to marketing authorisations in the Member States.

Impact

Benefit to public health by freeing up resources and by eliminating the current situation where industry avoids change or is non-compliant (to avoid the administrative burden). It is considered that there will be major costs savings for industry.

3.2.4. Rationalise risk management planning

Key changes to EU legislation

Clarify the existing legal requirement to submit a risk management plan at the time of the marketing authorisation application and make a clearer legal basis for risk management plans, including post-authorisation safety studies to be required when there is a public health concern. Ensure that the key risk management measures are included in the marketing authorisation thereby ensuring that marketing authorisation holders conduct the measures specified and provide updates to the competent authority and the EMEA as specified in the risk management plan.

Why

Currently risk management plans are requested but are not always agreed and when agreed the industry does not always comply with them (frequently post-authorisation safety studies are not conducted or completed). The legal basis for requesting risk management plans for authorised products is currently unclear and different authorities are using different legal provisions.

Impact

Commission Vice-President Günter Verheugen said in the Strategy announcement of February 2007 “*We will improve and strengthen the monitoring of the safety of medicines so that safety issues are rapidly detected, and effectively dealt with based on more robust data*”. These changes will be a major benefit to public health by ensuring that safety evaluation of products is prospective (i.e. based on risk management planning) and by ensuring that high-quality, EU safety studies are done (i.e. there is compliance) when justified by safety concerns.

The effect of the clarified legal provisions will be that risk management plans are only submitted when they are needed but that they are fully complied with. The proposals could be cost neutral for industry and national regulators as the proposals should lead to a reduction in poor quality risk management plans and poor compliance.

3.2.5. Codify oversight of non-interventional safety studies

Key changes to EU legislation

Codify guiding principles for the conduct of non-interventional post-authorisation safety studies (i.e. safety studies of marketed products that are not clinical trials). Light oversight (by EMEA pharmacovigilance committee only if conduct to be in more than one Member State) of non-interventional post-authorisation safety studies to ensure that they have health rather than promotional objectives.

Why

Studies are often of poor quality and frequently promotional. Currently there are no guiding principles and there is no oversight in EU legislation of non-interventional safety studies. There is an EU guideline but it does not ensure harmonised practice. Therefore there are divergent national measures (including legislation in some Member States) that interfere with the single market and make the conduct of these studies difficult.

Impact

Benefit to public health by ensuring that non-interventional safety studies are high-quality and non-promotional.

Possible cost reduction for industry as this will simplify the current divergences between Member States. For EMEA (new committee), see Section 3.2.1.

3.2.6. Simplify and make proportional reporting of single serious adverse drug reaction (ADR) case reports

Key changes to EU legislation

Simpler ADR reporting to reduce burden and free up resource:

- Ø all serious 3rd country reports go to the EU Eudravigilance database only,
- Ø all EU domestic reports go only to Eudravigilance and thereby to the Member State where they occurred,
- Ø the EMEA to take on new tasks, clearly defined in scope, for scanning of the scientific literature and entering case reports from the literature on Eudravigilance, rather than the duplication currently conducted by the industry.

Regarding medication errors the definition of adverse drug reaction would be clarified as would the reporting rules to make clear that medication errors that result in an adverse reaction should be reported to the competent authorities for medicines (and oblige Member States to ensure any Patient Safety authority is also notified).

To increase the proportionality between ADR reporting and the level of knowledge about the safety of a product and to allow a differentiated view of important new medicines, establish a European list of medicines under intensive monitoring: patients and healthcare professionals to be asked to report all suspected ADRs to these products. The EMEA will maintain a public list of intensively monitored products and removal from list will be linked to risk management plan milestones.

By fully capitalising on the EU pharmacovigilance database Eudravigilance and on electronic submission, there will be a significant decrease in the number of times an individual case report from a health professional or patient has to be submitted between the Marketing Authorisation Holders and the authorities and between the different authorities.

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

- Ø Patient adverse reaction reporting forms to be part of the patient information leaflet for intensively monitored drugs, with reports going to the Marketing Authorisation holder,
- Ø for all other drugs reporting via web-sites, directly to the national authority.

Why

The current ADR reporting rules are very complex and lead to heavy costs on industry and regulators. There is major scope for simplification by eradicating unnecessary duplication of reporting and by maximising the use of modern information technology.

Reporting to the authorities case reports of adverse reactions from the worldwide medical and scientific literature is currently an obligation on all companies leading to the same literature case report being submitted to multiple authorities by sometimes hundreds of companies (for generic medicinal products). Giving the core task for specific literature to the EMEA will reduce duplication of effort within the system and improve data quality in adverse reaction databases.

The need for patients to be empowered by allowing them to report the side effects they experience to their medicines was a key outcome of the 2006 public consultation.

EU medicines legislation is currently unclear on medication error reporting so that not all relevant safety data are available to assess the safety of medicines.

Impact

Benefit to public health by freeing up resource for both industry and regulators which can then be reinvested into efforts more closely linked to health protection and promotion. Empowering patients to report their side effects will increase their confidence in safety monitoring and the safety of medicines in general.

Changes on medication errors will benefit public health by ensuring that overdoses and medication errors are reported to the relevant authorities with a clear legal basis.

Major cost savings for industry and national regulators. Increase in costs to EMEA mainly from literature scanning.

3.2.7 Simplify and make proportional to risk periodic safety update report submission by industry (PSURs)

Key changes to EU legislation

Link PSURs to risk management planning and therefore the knowledge about the safety of the product. Where there is no risk management plan provide for periodicity of reporting to be proportional to the knowledge of safety i.e. no PSURs for old established products.

Balance this major reduction in routine periodic reporting by making clearer the current requirements on Marketing Authorisation Holders to report any changes in the benefits and risks of their products and to ensure the product information remains up to date.

Provide the legal basis for the existing Member State PSUR assessment work-sharing with a clear coordinating role for the new EMEA pharmacovigilance committee (the committee to: make public lists of reference dates for drug substances for the reporting cycle; requests for changes to the periodicity go from companies to the committee which approves changes; appoints the lead Member State for purely nationally authorised products; coordinates the assessment by the Member State; lead Member State gives the company the opportunity to comment on the assessment conclusions and EMEA makes public the Committee conclusions of the assessment).

Why

Currently major resource expended by industry and regulators with questionable public health benefit. Currently there is equal treatment of medicinal products whatever the perceived risk (due to limited correlation between risk and reporting). There is major duplication of reporting to different national authorities and duplication of assessment. Example: the hundreds of companies that have authorisations for aspirin products produce thousands of periodic reports which are submitted to the 30 EEA Member States.

Impact

Benefit to public health by freeing up resource and by reducing duplication of effort. Also there will be faster product safety assessment and faster updating of product information.

Major cost savings for industry and national regulators. For EMEA see Section 3.2.1 (new committee).

3.2.8.Strengthen medicines safety transparency and communication

Key changes to EU legislation

Codify legal and guideline provisions on transparency and communication. Communications about major new or changing safety issues - the principles to be laid down in law (with details in an implementing text) which would clarify roles and timing of communications.

For major safety issues including safety issues affecting drug substances authorised in more than one Member State the legal basis would be clarified for the EMEA committee to coordinate (but not replace) the communications of the Member States.

EMA should maintain an EU portal on the safety of medicines which would include links to websites of the Member State competent authorities.

Ensure that there are clear legal provisions on the provision of medicinal product information by companies including to support the development of an EU drug dictionary.

Why

Rules for both transparency and communications are partly in law and partly in guidelines and are not always coherent.

Communications about drug safety are frequently not coordinated at EU level leading to contradictory messages when patients access media from different Member States.

Impact

Benefit to public health by increasing the understanding and trust of patients and health professionals in the safety of medicines and the regulatory system. Clear, coordinated messages about specific safety risk issues will improve the safe use of medicines. Transparency will also increase the compliance of industry which will also benefit public health.

Cost neutral for industry. The EMA and National authorities will need to work on their existing websites. For EMA see Section 3.2.1 above.

3.2.9 Clearer safety warnings in product information to improve the safe use of medicines

Key changes to EU legislation

To allow patients to rapidly identify key messages, introduce a new section in the Summary of Product Characteristics and Patient Information Leaflet on 'key safety information' with a transitional phase of 5-years (i.e. update the product information at the time of the next renewal or the next major variation)

Why

The current organisation of product information makes it difficult to identify the most important safety warnings: this results in a risk that key safety measures / warnings may be missed.

Impact

Major benefit to public health by ensuring that key safety information is highlighted maximising the chances of it being read, understood and leading to risk minimisation.

Costs minimal as the introduction of the key safety warnings in product information would be at the existing product 'renewal' or when other labelling reviews are conducted.

Section 4 Detailed proposals to change EU legal texts

The detailed proposals for changes to the legislation are presented in Annex 1 and a summary 'Table of correspondence' is at Annex 2.

In Annex 1:

- The detailed text changes are presented for Directive 2001/83/EC.
- Those legal provisions that are currently the same or similar in Regulation (EC) No 726/2004 to Directive 2001/83/EC are not presented in detail in Section 4, however, these provisions will be updated by analogy.
- In contrast, provisions specific to Regulation (EC) No 726/2004 are presented.

**Pharmaceuticals Unit
DG Enterprise and Industry
European Commission
4 December 2007**

ANNEX 1
Strategy to Better Protect Public Health by Strengthening and Rationalising EU Pharmacovigilance:
Detailed proposals for legislative changes

The detailed proposals for changes to the legislation are presented in this Annex. The detailed text changes are presented for Directive 2001/83/EC. Those legal provisions that are currently the same or similar in Regulation (EC) No 726/2004 to Directive 2001/83/EC are not presented in detail in this Annex, however, these provisions will be updated by analogy. In contrast, provisions specific to Regulation (EC) No 726/2004 are presented.

Drafting Code: Existing text, and proposed text which is unchanged from the existing text, is presented in regular font style. Where it is proposed to delete existing text the deleted text is presented as ~~striketrough~~. Where new text is proposed this text is underlined. Where extensive sections of new text replace existing sections then this is made clear and striketrough and underlining are not used.

Current	Proposed
Directive 2001/83/EC Article 1(11) Adverse reaction: A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.	Directive 2001/83/EC Article 1(11) Adverse reaction: A response to a medicinal product which is noxious and unintended. and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.
Directive 2001/83/EC Article 1(13) Unexpected adverse reaction: An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.	Directive 2001/83/EC Article 1(13) Unexpected adverse reaction: An adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics.
Directive 2001/83/EC Article 1(16) Abuse of medicinal products: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.	Directive 2001/83/EC Article 1(16) Abuse of medicinal products: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
Directive 2001/83/EC Article 1(15)	Directive 2001/83/EC Article 1(15)

Post-authorisation safety study: A pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product.	Post-authorisation safety study: A pharmacoepidemiological study or a clinical trial with an authorised medicinal product in accordance with the terms of the marketing authorisation, conducted with the aim of identifying, <u>characterising</u> or quantifying a safety hazard <u>or confirming the safety profile of the medicinal product.</u>
	Directive 2001/83/EC Article 1(33) <u>Risk management system: a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a specific medicinal product, including the assessment of the effectiveness of those interventions.</u>
	Directive 2001/83/EC Article 1(34) <u>Pharmacovigilance System Master File: A detailed description of the pharmacovigilance system utilized by the marketing authorisation holder to fulfill the tasks and responsibilities listed in Title IX with respect to one or more authorised medicinal product.</u>
Directive 2001/83/EC Article 8 (3)(ia) A detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the applicant will introduce.	<p>Directive 2001/83/EC Article 8 (3)(ia) A detailed description <u>summary</u> of the pharmacovigilance <u>system which shall include: 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 qualified person to the effect that the applicant has the necessary means to fulfill the tasks and responsibilities listed in Title IX, and a reference to the site of the Pharmacovigilance System Master File for the medicinal product. and, where appropriate, of the risk management system which the applicant will introduce.</u></p> <p>Directive 2001/83/EC Article 8 (3)(iaa) A detailed description of the pharmacovigilance and, where appropriate, of the risk-management system which the a pplicant will introduce. <u>This</u></p>

	<u>risk management system shall be proportionate to the identified and potential risks taking into consideration the information available on the medicinal product.</u>
<p>Directive 2001/83/EC Article 8 (3)(n)</p> <p>Proof that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.</p>	<p>Directive 2001/83/EC Article 8(3)(n)</p> <p>Proof that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.</p>
<p>Directive 2001/83/EC Article 11</p> <p>The summary of the product characteristics shall contain, in the order indicated below, the following information:</p> <ol style="list-style-type: none"> 1. name of the medicinal product followed by the strength and the pharmaceutical form. 2. qualitative and quantitative composition in terms of the active substances and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product. The usual common name or chemical description shall be used. 3. pharmaceutical form. 	<p>Directive 2001/83/EC Article 11</p> <p>The summary of the product characteristics shall contain, in the order indicated below, the following information:</p> <ol style="list-style-type: none"> 1. name of the medicinal product followed by the strength and the pharmaceutical form. 2. qualitative and quantitative composition in terms of the active substances and constituents of the excipient, knowledge of which is essential for proper administration of the medicinal product. The usual common name or chemical description shall be used. 3. pharmaceutical form. <p><u>3b. key safety information about the medicinal product and how to minimise risks. For medicinal products included on the European list of intensively monitored products referred to in Article 101j this information shall also include the statement “This medicinal product is under intensive monitoring. All suspected adverse reactions should be reported”.</u></p>
Directive 2001/83/EC Article 21	Directive 2001/83/EC Article 21

<p>1. When the marketing authorization is issued, the holder shall be informed, by the competent authorities of the Member State concerned, of the summary of the product characteristics as approved by it.</p> <p>2. The competent authorities shall take all necessary measures to ensure that the information given in the summary is in conformity with that accepted when the marketing authorization is issued or subsequently.</p> <p>3. The competent authorities shall make publicly available without delay the marketing authorisation together with the summary of the product characteristics for each medicinal product which they have authorised.</p> <p>4. The competent authorities shall draw up an assessment report and comments on the file as regards the results of the pharmaceutical and pre-clinical tests and the clinical trials 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.</p> <p>The 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.</p> <p>[Regulation (EC) No 726/2004 Article 9]</p>	<p>1. When the marketing authorization is issued, the holder shall be informed, by the competent authorities of the Member State concerned, of the summary of the product characteristics as approved by it.</p> <p><u>The risk management system shall be annexed to the marketing authorisation.</u></p> <p>2. The competent authorities shall take all necessary measures to ensure that the information given in the summary is in conformity with that accepted when the marketing authorization is issued or subsequently.</p> <p>3. The competent authorities shall make publicly available without delay the marketing authorisation together with the summary of the product characteristics for each medicinal product which they have authorised.</p> <p>4. The competent authorities shall draw up an assessment report and comments on the file as regards the results of the pharmaceutical and pre-clinical tests and the clinical trials <u>and as regards the risk management system</u> 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.</p> <p>The 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.</p>
<p>Directive 2001/83/EC Article 22</p> <p>In exceptional circumstances and following consultation with the applicant, the authorisation may be granted subject to a requirement for</p>	<p>Directive 2001/83/EC Article 22</p>

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 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. The list of these conditions shall be made publicly accessible without delay, together with deadlines and dates of fulfilment.

[Regulation (EC) No 726/2004 Article 9(4)(c), 14(8)]

~~1. In exceptional circumstances and following consultation with the applicant, the authorisation~~ A marketing authorisation may be granted subject to the following conditions, included in the risk management system: ~~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 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. The list of these conditions shall be made publicly accessible without delay, together with deadlines and dates of fulfilment.

- (a) the requirement to conduct post-authorisation safety studies, or,
- (b) adverse reaction recording or reporting that differs from the requirements of Title IX, or,
- (c) any conditions or restrictions with regard to the safe and effective use of the medicinal product.

The marketing authorisation shall lay down dead-lines for the fulfilment of the conditions where necessary. Continuation of the authorisation shall be linked to the fulfilment of these conditions and the assessment of any data resulting from the implementation of the conditions.

2. The Member States shall notify to the Agency the granting of marketing authorisations subject to conditions as referred to in paragraph 1 and these medicinal products shall be included in the European list of intensively monitored products referred to in Article 101j.

A medicinal product shall be removed from the list when the competent authority which granted the marketing authorisation concludes that the measures referred to in paragraph 1 have been completed and that,

	<u>following the assessment of any data resulting from the implementation of the conditions, the benefit -risk balance remains positive.</u>
<p>Directive 2001/83/EC Article 23</p> <p>After an authorization has been issued, the authorization holder must, 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.</p> <p>These changes shall be subject to the approval of the competent authority of the Member State concerned.</p> <p>The authorisation holder shall forthwith supply to the 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.</p> <p>In particular, he shall forthwith inform the 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.</p> <p>In order that the risk-benefit balance may be continuously assessed, the competent authority may at any time ask the holder of the marketing authorisation to forward data demonstrating that the risk -benefit balance remains favourable.</p> <p>[Regulation (EC) No 726/2004 Article 16]</p>	<p>Directive 2001/83/EC Article 23</p> <p>After an authorization has been issued, the authorization holder must, 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.</p> <p>These changes shall be subject to the approval of the competent authority of the Member State concerned.</p> <p>The authorisation holder shall forthwith supply to the 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.</p> <p>In particular, he shall forthwith inform the 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, <u>including results of clinical trials</u>, which might influence the evaluation of the benefits and risks of the medicinal product for human use concerned. <u>He shall ensure that the product information is kept up to date with the current scientific knowledge including assessment conclusions made public via the European medicines safety web-portal referred to in Article 101i.</u></p> <p>In order that the risk-benefit balance may be continuously assessed, the competent authority may at any time ask the holder of the marketing authorisation to forward data demonstrating that the risk -benefit balance</p>

	<p>remains favourable.</p> <p><u>The competent authority may at any time ask the holder of the marketing authorisation to submit a copy of the pharmacovigilance system master file.</u></p>
<p>Directive 2001/83/EC Article 26</p> <p>1. The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8, 10, 10a, 10b and 10c, it is clear that:</p> <p>(a) the risk-benefit balance is not considered to be favourable; or</p> <p>(b) its therapeutic efficacy is insufficiently substantiated by the applicant; or</p> <p>(c) its qualitative and quantitative composition is not as declared.</p>	<p>Directive 2001/83/EC Article 26</p> <p>1. The marketing authorisation shall be refused if, after verification of the particulars and documents listed in Articles 8, 10, 10a, 10b and 10c, it is clear that:</p> <p>(a) the risk-benefit balance is not considered to be favourable; or</p> <p>(b) its therapeutic efficacy is insufficiently substantiated by the applicant; or</p> <p>(b) its qualitative and quantitative composition is not as declared.</p>

<p>Direction 2001/83/EC Article 31</p> <p>1. 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, in particular to take account of the information collected in accordance with Title IX.</p>	<p>Direction 2001/83/EC Article 31</p> <p>1. 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, in particular to take account of the information collected in accordance with Title IX.</p> <p><u>However, where one of the criteria listed in Article 10 1k are met the procedure of that Article shall be followed.</u></p>
<p>Direction 2001/83/EC Article 36</p> <p>1. Where a Member State considers that the variation of a marketing authorization which has been granted in accordance with the provisions of this Chapter or its suspension or withdrawal is necessary for the protection of public health, the Member State concerned shall forthwith refer the matter to the Agency for the application of the procedures laid down in Articles 32, 33 and 34.</p>	<p>Direction 2001/83/EC Article 36</p> <p>1. Where a Member State considers that the variation of a marketing authorization which has been granted in accordance with the provisions of this Chapter or its suspension or withdrawal is necessary for the protection of public health, the Member State concerned shall forthwith refer the matter to the Agency for the application of the procedures laid down in Articles 32, 33 and 34.</p> <p><u>However, where one of the criteria listed in Article 101k are met the procedure of that Article shall be followed.</u></p>
<p>Direction 2001/83/EC Article 54</p> <p>The following particulars shall appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging:</p>	<p>Direction 2001/83/EC Article 54</p> <p>The following particulars shall appear on the outer packaging of medicinal products or, where there is no outer packaging, on the immediate packaging:</p>

	<p><u>(o) For medicinal products included on the European list of intensively monitored products referred to in Article 101j, the following statement shall be included “All suspected adverse reactions should be reported (see leaflet for details)”.</u></p>
<p>Direction 2001/83/EC Article 5 9</p> <p>1. The package leaflet shall be drawn up in accordance with the summary of the product characteristics; it shall include, in the following order:</p> <p>(a) for the identification of the medicinal product:</p> <p>(i) the name of the medicinal product followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults. The common name shall be included where the product contains only one active substance and if its name is an invented name;</p> <p>(ii) the pharmaco-therapeutic group or type of activity in terms easily comprehensible for the patient;</p> <p>(b) the therapeutic indications;</p>	<p>Direction 2001/83/EC Article 5 9</p> <p>1. The package leaflet shall be drawn up in accordance with the summary of the product characteristics; it shall include, in the following order:</p> <p>(a) for the identification of the medicinal product:</p> <p>(i) the name of the medicinal product followed by its strength and pharmaceutical form, and, if appropriate, whether it is intended for babies, children or adults. The common name shall be included where the product contains only one active substance and if its name is an invented name;</p> <p>(ii) the pharmaco-therapeutic group or type of activity in terms easily comprehensible for the patient;</p> <p>(b) the therapeutic indications;</p> <p><u>(ba) key safety information about the medicinal product and how to minimise risks. This information shall be presented in a box surrounded by a black border. For medicinal products included on the European list of intensively monitored products referred to in Article 101j the following additional statement shall be included “This medicinal product is under intensive monitoring. All suspected adverse reactions should be reported to < the name and address of the marketing authorisation holder</u></p>

	in the Member State where the marketing authorisation holder will receive suspected adverse reaction reports >”
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Directive 2001/83/EC Title IX (Articles 101 – 108) ‘Pharmacovigilance’ to be replaced with the following text [with equivalent changes to Regulation (EC) No 726/2004 Article 20 and 21 - 29]

CHAPTER 1

Reporting of adverse reactions by healthcare professionals and identification of biological medicinal products which are the subject of adverse reaction reports

Article 101a

The Member States shall take all appropriate measures to encourage doctors and other health care professionals to report suspected adverse reactions to the marketing authorisation holder or the competent authorities.

The Member States may impose specific requirements on doctors and other health care professionals in respect of the reporting of suspected serious or unexpected adverse reactions.

Through the methods of collecting information and where necessary through the follow up of adverse reaction reports, the Member States shall ensure that any biological medicinal product prescribed and dispensed in their territory which is the subject of an adverse reaction report is identifiable.

CHAPTER 2

Good Vigilance Practice

Article 101b

1. Following consultation with the Agency, Member States and interested parties, and in accordance with the procedure referred to in Article 121 (2), the Commission may adopt guidelines on good pharmacovigilance practice including technical rules and procedures for :

- Ø the use of internationally agreed terminologies, including medical terminologies, for formats and standards for the conduct of pharmacovigilance.
- Ø the electronic reporting of adverse reactions and the submission of reports to Eudravigilance in accordance with Article 101e
- Ø the monitoring by the Agency of the data in Eudravigilance for signals of new or changing risks in accordance with 101d.
- Ø the format of periodic safety update reports submitted in accordance with Article 101f.
- Ø the format of protocols and final study reports for the post-authorisation safety studies referred to in Art 101h.
- Ø Procedures and formats for drug safety communications including the procedures for management of urgent communications in accordance with Article 101i.
- Ø the operation of Article 101k.
- Ø Scientific and procedural guidelines on audit by the Marketing Authorisation Holders, National Competent Authorities and Agency of their performance of pharmacovigilance.

These guidelines shall be revised as necessary to take account of technical and scientific progress.

2. Marketing authorisation holders, the Agency and the competent authorities shall follow the guidelines referred to in paragraph 1 in the fulfilment of their tasks related to pharmacovigilance.

3. The measures adopted shall take account of international harmonisation work carried out in the field of pharmacovigilance.

CHAPTER 3

Independence

Article 101c

The management of funds intended for activities connected with pharmacovigilance, the operation of communication networks and market surveillance shall be under the permanent control of the competent authorities in order to guarantee their independence. These requirements do not preclude the collection of fees charged to marketing authorisation applicants or marketing authorisation holders for these activities.

CHAPTER 4

Data management and reporting

Section 1

Eudravigilance and recording and reporting of adverse reactions

Article 101d

1. The Agency, in collaboration with the Member States and the Commission, shall set up and maintain the European pharmacovigilance database and data-processing network (hereinafter “Eudravigilance”) to facilitate the exchange of pharmacovigilance information regarding medicinal products authorised in accordance with Article 6(1) in order to allow all competent authorities to share the information at the same time.
2. The Agency, in collaboration with the Member State Competent Authorities, shall monitor the data in Eudravigilance for signals of new or changing risks of medicinal products authorised in the Community. In the event of a change being detected the Agency shall inform the marketing authorisation holder, the Member States and the Commission of these findings.
3. Individual adverse reaction reports held on the Eudravigilance database may be requested by the public and these data shall be provided by the Agency or the national competent authority from whom they were requested within 90 -days unless this would compromise the anonymity of the subjects of the reports.

Article 101e

1. Marketing authorisation holders shall record all adverse reactions in the Community or in third countries which are brought to their attention. Adverse reactions recorded shall be reports where the Marketing Authorisation Holder considers that a causal relationship is at least a reasonable possibility, and this shall include:
 - (a) Reports where the Patient or the Healthcare Professional has made a statement that a causal relationship between the event and the medicinal product is considered to be at least a reasonable possibility; and
 - (b) Reports where the Patient or the Healthcare Professional has not made any statement on the suspected causal relationship or has stated that the causal relationship is unknown but the temporal relationship between the exposure to the medicinal product and the adverse reaction means that a causal relationship can not be excluded.

The marketing authorisation holder shall accept reports of adverse reactions electronically.

These reports shall be collated at one point within the Community.

2. Marketing authorisation holders shall submit electronically to Eudravigilance, no later than 15-days following the receipt of the report, all adverse reactions that occur in the Community and all serious adverse reactions that occur outside the Community .

These reports will be made available to the Member State through Eudravigilance.

3. The Member States shall record all adverse reactions that occur in their territory which are brought to their attention from healthcare professionals and patients. Member States shall submit electronically to Eudravigilance and to the marketing authorisation holders all of these reports which meet the notification criteria in accordance with the guidelines referred to in Article 101b.

To facilitate the reporting of suspected adverse reactions by healthcare professionals and patients each Member State shall accept reports of adverse reactions via their websites which shall be linked to the European medicines safety web -portal referred to in Article 101i.

The Member States shall ensure that reports of medication errors brought to their attention in the framework of adverse reaction reporting for medicinal products are made available to any national competent authorities for patient safety within that Member State. They shall also ensure that the national competent authorities for medicinal products are notified of any adverse reactions brought to the attention of national competent authorities for patient safety.

4. By -/- (5-years after the entry into force of this directive), the Agency, in collaboration with the Member States shall make available web-based structured reporting forms for European healthcare professionals and patients to facilitate electronic reporting of adverse reactions and submission to Eudravigilance.

5. The Agency shall monitor medical literature for reports of adverse reactions to medicinal products for human use authorised or registered in the Community. It shall publish the list of publications subject to this monitoring, and it shall enter into Eudravigilance relevant information from the identified literature.

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 Eudravigilance.

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

Article 101f

1. Marketing authorisation holders shall submit periodic safety update reports to the Agency containing a scientific evaluation of the risk-benefit balance of the medicinal product on the basis of all available data. Periodic safety update reports shall present summaries of data relevant to the benefits and risks of the medicinal product and shall not routinely contain listings of individual case reports already submitted to Eudravigilance. Periodic safety update reports shall also contain 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.

2. The frequency and dates of submission of the periodic safety update reports shall be :

- a) Specified in accordance with paragraph 4, or
- b) Specified as a condition of the granting of the marketing authorisation, or
- c) In the absence of specification pursuant to either point a) or b) above, immediately upon request or at least every six months after authorisation and until the placing on the market. Thereafter, periodic safety update reports shall be submitted immediately upon request or at least every six months during the first two years following the initial placing on the market and once a year for the following two years. Thereafter, the reports shall be submitted at three-yearly intervals, or immediately upon request.

Reports shall be submitted electronically.

3. Unless other requirements have been laid down as a condition for the granting of the marketing authorisation, the requirements of paragraphs 1 and 2 shall not apply to products authorised in accordance with Articles 10, 10a, 10c, 13 to 16 or 16a to 16i of Directive 2001/83/EC.

This derogation from paragraphs 1 and 2 shall not apply to products of biological origin.

4. The following rules shall apply to the submission and assessment of periodic safety update reports:

- (a) the Committee on Pharmacovigilance referred to in Article 56(a) of Regulation EC(No) 726/2004 may determine the European reference dates and frequency of submission for periodic safety update reports for certain medicinal products for human use authorised in the

Community. For the purposes of this provision, the European reference date for products containing the same active substance shall be the date of the first authorisation in the Community of a medicinal product containing that substance. The same applies if the date of the first authorisation in the Community cannot be determined.

- (b) the Committee shall draw up and maintain a list of European reference dates and frequency and dates of submission fixed in accordance with point (a) above, which shall be made public by the Agency via the European medicines safety web-portal referred to in Article 101i.
- (c) marketing authorisation holders for medicinal products requiring periodic safety update reports may submit requests to the Committee on Pharmacovigilance to change the European reference date or submission schedule for periodic safety update reports. The Committee on Pharmacovigilance shall have the authority to change the reference date and the submission schedule even when these are conditions of the marketing authorisation and the schedule shall be made public by the Agency via the European medicines safety web-portal referred to in Article 101i.
- (d) by way of derogation of paragraph 3 above, the Committee may request a periodic safety update report for products referred to in that paragraph in case of a suspected pharmacovigilance risk.
- (e) the Committee shall appoint a member state or a rapporteur of that Committee to be responsible for the periodic safety update report assessment. When selecting the member state or rapporteur the Committee shall take into account whether any competent authority of a Member State is acting, in accordance with Article 28(1), as a reference member state, or, for centrally authorised products, the rapporteur of the Committee for Human Medicinal Products,
- (f) the Member State or rapporteur responsible for the periodic safety update report assessment shall produce an assessment report within 90 days of receipt of the periodic safety update report and this shall be sent to the marketing authorisation holder and the Committee on Pharmacovigilance. Within 30-days of receiving the assessment the marketing authorisation holder may submit comments on it to the Member State or rapporteur and the Committee on Pharmacovigilance.
- (g) Taking into account any comments submitted, at its next meeting the Committee on Pharmacovigilance shall adopt the assessment report with or without changes to its conclusions.
- (h) The assessment conclusions shall be made public including any recommendations for the product information by the Agency via the European medicines safety web-portal referred to in Article 101i.
- (i) Competent authorities and marketing authorisation holders shall take account of the recommendations for the product information.

Section 2

Post-authorisation safety studies

Article 101g

1. The competent authority which granted the marketing authorisation may require a marketing authorisation holder to conduct a post-authorisation safety study if there are serious concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. Any requirement shall:

- (a) be made in writing,
- (b) provide a detailed justification,
- (c) include the objectives and timeframe for submission and conduct of the study.

2. The 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 competent authority may withdraw the requirement or issue a final requirement.

4. Requirements for post-authorisation safety studies shall be included as a condition of the marketing authorisation.

Article 101h

1. The following provisions shall apply to non-interventional post-authorisation safety studies that are initiated, managed or financed by the marketing authorisation holder and that involve the collection of data from patients or healthcare professionals and that do not fall within the scope of Directive 2001/20/EC:

- a) The studies shall not be performed where the act of conducting the study promotes the use of a medicinal product.
- b) Payments to healthcare professionals for participating in the studies shall be restricted to compensation of time and expenses incurred.
- c) A draft protocol shall be submitted to the national competent authority for studies to be conducted in only one Member State, and to the Committee on Pharmacovigilance referred to in Article 56(a) of Regulation (EC) No 726/2004 for studies to be conducted in more than one Member State.
- d) In the absence of a letter of objection from the competent authority or the Committee, as appropriate, within 60-days of the submission date, the study may commence. In the event that the competent authority or the Committee, as appropriate, objects to the study protocol because it is considered to fall under the scope of Directive 2001/20/EC, or because the conduct of the study is considered to promote the use of a

medicinal product, the marketing authorisation holder shall be informed in writing with detailed grounds. In this event the study shall not commence until the competent authority or the Committee has given its written approval.

- e) The competent authority or the Committee, as appropriate, may give a recommendation on the submitted protocol within 60 -days. The marketing authorisation holder shall take this recommendation into account before commencing the study.
- f) After a study has commenced major amendments to the protocol shall be notified to the competent authority or the Committee, as appropriate.
- g) 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 competent authority in accordance with Article 23.
- h) The submission of final study reports and the reporting of adverse reactions from the studies shall be specified in the study protocol.
- i) The marketing authorisation holder shall consider whether the results of the study impact on the product labelling and submit an application to vary the product labelling to the competent authorities.
- j) In addition to any reporting requirements in the study protocol, the marketing authorisation holder shall submit an abstract of the study results to the Committee. The Committee may decide that the abstract is made public via the European medicines safety web -portal referred to in Article 101i or, after the agreement of the marketing authorisation holder, may decide that an amended abstract shall be made public.
- k) Based on the results of studies the Committee may make recommendations for the product information and these shall be made public via the Agency web-portal.
- l) Competent authorities and marketing authorisation holders shall take account of the recommendations for the product information.

CHAPTER 5

Communications

Article 101i

1. The Agency shall set up and update a European medicines safety web -portal in collaboration with the Member States and the Commission. By means of the European medicines safety web -portal, the Agency shall make public at least the following information:

- (a) The members of the committees referred to in Article 56(1)(a) and 56(1)(a)a of Regulation EC (No) 726/2004 together with their professional qualifications and declarations of any specific interests.
- (b) A summary of the conclusions and recommendations relating to pharmacovigilance activities from each meeting of the committees listed in point (a).

- (c) Information about how to report suspected adverse reactions to medicinal products and forms for their web-based reporting by patients, healthcare professionals and marketing authorisation holders.
- (d) Agreed risk management plans pursuant to Articles 22 and 101p for medicinal products authorised in accordance with Regulation (EC) No 726/2004.
- (e) The intensive monitoring list referred to in Article 101j.
- (f) A list of marketing authorisation holder qualified persons for pharmacovigilance and the Member State in which they reside.
- (g) Reference dates for the reporting of periodic safety update reports and conclusions and recommendations for product information from the assessment of periodic safety update reports.
- (h) Agreed post-authorisation safety study protocols, the public abstracts and any recommendations for product information in accordance with Article 101g.
- (i) The initiation of the procedure of Article 101k, the substances or products concerned and the issue being addressed, the public hearings pursuant to that procedure and information on how to submit information and to participate in these public hearings.

2. Each Member State shall set up and update a national medicines safety web-portals which shall be linked to the European medicines safety web-portal referred to in paragraph 1. By means of the national medicines safety web-portals, the Member States shall make public at least the following information:

- (a) Agreed risk management plans pursuant to Articles 22 and 101p for medicinal products authorised in accordance with the procedures of this directive.
- (b) The intensive monitoring list referred to in Article 101j.

3. As soon as the holder of a marketing authorisation has the intention to make a public announcement relating to important information on pharmacovigilance concerns including product withdrawals and major restrictions to the use of a product he shall give notification to the Member State competent authorities, the Agency and the Commission. The marketing authorisation holder shall ensure that such information is presented objectively and is not misleading.

4. Unless urgent public announcements are required for the protection of public health, the Member States, the Agency and the Commission shall give each other notification not less than twenty-four hours prior to a public announcement relating to important information on pharmacovigilance concerns including product withdrawals and major restrictions to the use of a product.

5. For substances authorised as medicinal products in more than one Member State, the Agency shall be responsible for the coordination between competent authorities of important 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 common safety messages and distribution timetables.

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

Article 101j

The Agency shall establish and make public a list of medicinal products for human use under intensive monitoring. This list shall include the names and active substances of medicinal products referred to in Article 22(2) and an electronic link to the product information. The Agency shall maintain the list up to date.

CHAPTER 6

Community assessment and binding decisions

Article 101k

1. A Member State shall notify the other Member States, the Agency and the Commission and shall thereby initiate the procedure of this article where:

- a) it considers the suspension or revocation of a marketing authorisation, or it has suspended a marketing authorisation.
- b) it considers suspending the marketing or distribution of a medicinal product, or it has suspended the marketing or distribution of a medicinal product.
- c) it considers refusing the renewal of a marketing authorisation.
- d) it is informed by the marketing authorisation holder of its intention to withdraw, or of the fact that it has withdrawn, a medicinal product from the market on the basis of safety concerns.
- a) it considers that new contraindications, a reduction in the recommended dose, or a restriction to the indications is necessary.
- e) it has conducted a pharmacovigilance inspection and found serious deficiencies.

2. Where urgent action to protect public health is necessary, the Member State concerned may suspend the marketing authorisation of a medicinal product. It shall inform the Agency, the Commission and the other Member States not later than the following working day.

3. The notifications under paragraph 1 may relate to individual medicinal products, or to groups of medicinal products identified by the substances they contain. If the Agency identifies that the issue notified relates to more medicinal products than are included in the notification or is common to all products containing a substance then the Agency may enlarge the scope of the procedure accordingly.

5. At the time of the notification under paragraph 1 the Member State shall make available to the Agency all scientific information available to it relevant to the notification and any assessment by the Member State.

6. Following notification under paragraph 1 or 2, within two working days the Agency shall publicly announce the initiation of the procedure via the web-portal referred to in Article 101i. This announcement shall specify the matter notified, the medicinal products or substances concerned and how information relevant to the procedure can be submitted. This announcement shall serve to inform marketing authorisation holders and the public of the procedure and their right to submit to the Agency information relevant to the procedure.

Where a public hearing is to be held pursuant to paragraph 7, the announcement shall include information on the public hearing and how marketing authorisation holders and the public can participate.

7. Except when urgent action is required for the protection of public health, the Committee on Pharmacovigilance shall hold a public hearing on the matter notified and marketing authorisation holders and the public may participate by registering following the public announcement of paragraph 5. The Agency shall ensure that all those who register have the opportunity to participate either in person or through the use of web-based technology.

8. Where a marketing authorisation holder has commercially confidential data relevant to the issue of the procedure, he may request to present those data to the Committee on Pharmacovigilance in a non-public hearing.

9. The Committee on Pharmacovigilance shall assess the matter notified and make a recommendation to the Committee for Medicinal Products for Human Use referred to in Article 56(1)(a) of Regulation EC (No) 726/2004.

10. No later than 90-days following notification under paragraph 1 and following the recommendation referred to in paragraph 9, the Committee for Medicinal Products for Human Use shall adopt an opinion on the notified safety or risk-benefit concern. This opinion may include:

- a) That no further evaluation or action is required at Community level.
- b) That the marketing authorisation holder should conduct further evaluation of data together with the follow up of the results of that evaluation.

- c) That the marketing authorisation holder should sponsor a post -authorisation safety study together with the follow up evaluation of the results of that study.
- d) That the Member States need to implement risk minimisation actions and the nature of those actions.
- e) Suspension, revocation, or non -renewal of the marketing authorisation.
- f) Changes to the product information of the medicinal products concerned which shall specify specific wording and where such wording shall be placed in the summary of the product characteristics .

The opinion shall be made public.

11. Acting on the basis of the opinion of paragraph 10, the Commission may request the Member States in which the product is authorised to take temporary measures immediately.

12. Unless the opinion of paragraph 10 is that no further evaluation or action is required at Community level , the Commission shall adopt a final decision addressed to the Member States in accordance with the procedure referred to in Article 121(2) .

CHAPTER 7

Responsibilities and tasks

Article 101l

1. In addition to the general responsibilities for pharmacovigilance laid down in Article 57 (1)(c) of Regulation EC(No) 726/2004 and the specific responsibilities and tasks laid down in Articles 101a to 101k above, the Agency shall:

- (a) Maintain a public register of any pharmacovigilance tasks delegated by one Member State to another or to the Agency, as referred to in Article 101l(2).
- (b) Upon the request of the Commission, participate, in collaboration with the Member States, in international harmonization and standardization of technical measures in pharmacovigilance.
- (c) Perform regular audit of its pharmacovigilance tasks and report the results to its Management Board on a yearly basis.
- (d) In collaboration with marketing authorisation holders and the Member States, monitor the outcome of risk minimization measures relating to centrally authorised products and those which are the outcome of the procedure of Article 101k.

- (e) As documented in the risk management system assess updates to the risk management system or any data resulting from the measures contained therein.
- (f) Advise on drug safety communication s.

2. In addition to the general responsibilities as competent and supervisory authority and the specific responsibilities and tasks laid down in Articles 101a to 101k above, the Member States shall:

- a) Designate a competent authority for the conduct of pharmac ovigilance.
- b) Designate a supervisory authority for pharmacovigilance inspections.
- c) If the qualified person for pharmacovigilance for a centrally authorised product resides in that Member State then the Member State shall act as the supervisory authority for pharmacovigilance inspections.
- d) Operate a pharmacovigilance system to collect information useful in the surveillance of medicinal products, with particular reference to adverse reactions in human beings and evaluating such information scientifically. The sy stem shall have the ability to identify the medicinal products prescribed and dispensed which are the subjects of an adverse reaction report.
- e) Monitor data in Eudravigilance for signals of new or changing risks and for changes to the risk benefit balance o f medicinal products for which it is the competent authority and where no reference member state exists.
- f) In collaboration with the marketing authorisation holders, monitor the outcome of risk minimization measures relating to nationally authorised products.
- g) Upon the request of the Commission and under the coordination of the Agency, participate in international harmonization and standardization of technical measures in pharmacovigilance.
- h) Perform regular audit of its pharmacovigilance tasks including its pe rformance of Good Vigilance Practices and report the results to the European Commission no later than -/- (two-years after the entry into force of this directive) and then yearly thereafter.

Any of the tasks specified in Article s 101 a to 101l may be delegated by one Member State to another Member State with the written agreement of that Member State. In this event, the delegating Member State shall inform the Commission, the Agency and all other Member States in writing. This information shall be made pub lic by the Member State concerned and by the Agency.

3. No later than -/- (three-years after the entry into force of this direct ive) and then yearly thereafter, t he Commission services shall make public a report on the conduct of pharmacovigilance by the Member States.

4. In addition to the general responsibilities for monitoring the benefit risk balance of the product, for notifying new information including clinical trial results and keeping product information up to date pursuant to Article 23, and the specific responsibilities and tasks laid down in Articles 101a to 101k above, the Marketing Authorisation holder shall:

- a) Have permanently and continuously at his disposal an appropriately qualified person responsible for pharmacovigilance. That qualified person shall reside in the Community and shall be responsible for the establishment and maintenance of the pharmacovigilance system which shall cover the tasks listed in this paragraph. The name and contact details of the qualified person shall be notified to the competent authority and the agency.
- b) Operate a pharmacovigilance system which shall cover the tasks listed in this paragraph.
- c) Maintain and make available on request a pharmacovigilance system master file.
- d) Monitor all available relevant data including data on Eudravigilance for signals of new or changing risks and for changes to the risk benefit balance of the medicinal product.
- e) Maintain and follow the risk management system for the medicinal product including all risk minimization measures included in the risk management system and the marketing authorisation.
- f) Perform regular audit of its pharmacovigilance tasks including its performance of Good Vigilance Practices and place a report of the audit on the pharmacovigilance system master file.

5. For medicinal products authorised in accordance with the provisions of Chapter IV, the tasks listed in paragraph 2(e), and (f) shall be performed by the reference Member State.

CHAPTER 8

General provisions

Article 101m

The Agency shall collaborate with the World Health Organisation in matters of international 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; it shall send a copy thereof to the Member States.

Article 101n

The Agency and Member States' competent authorities 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 101o

Member States shall take the necessary measures to ensure that a marketing authorisation holder who fails to discharge the obligations contained in this Title is subject to effective, proportionate and dissuasive penalties.

Article 101p

1. In the case of medicinal products authorised -/- [after the entry into force of this directive], the competent authority which granted the marketing authorisation may require a marketing authorisation holder to submit a risk management system if there are concerns about the risks affecting the risk-benefit balance of an authorised medicinal product. Any requirement shall:

- (d) be made in writing,
- (e) provide a detailed justification,
- (f) include the timeframe for submission and agreement.

2. The 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 requirement

3. On the basis of explanations submitted by the marketing authorisation holder, the competent authority may withdraw the requirement or issue a final requirement.

Article 101q

The Commission shall adopt any amendments which may be necessary to update the provisions of Articles 101 a to 101p to take account of scientific and technical progress. These 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).

<p>Direction 2001/83/EC Article 111</p> <p>1. The competent authority of the Member State concerned shall ensure, 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, that the legal requirements governing medicinal products are complied with.</p> <p>The competent authority may also carry out unannounced inspections at the premises of manufacturers of active substances used as starting materials, or at the premises of marketing authorisation holders whenever it considers that there are grounds for suspecting non-compliance with the principles and guidelines of good manufacturing practice referred to in Article 47. These inspections may also be carried out at the request of a Member State, the Commission or the Agency.</p> <p>In order to verify whether the data submitted in order to obtain a conformity certificate comply with the monographs of the European Pharmacopoeia, the standardisation body of the nomenclatures and the quality norms within the meaning of the Convention relating to the elaboration of the European Pharmacopoeia ⁴ (European Directorate for the quality of Medicinal Products) may ask the Commission or the Agency to request such an inspection when the starting material concerned is the subject of a European Pharmacopoeia monograph.</p> <p>The competent authority of the Member State concerned may carry out</p>	<p>Direction 2001/83/EC Article 111</p> <p>1. The competent authority of the Member State concerned shall ensure, 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, that the legal requirements governing medicinal products are complied with.</p> <p>The competent authority may also carry out unannounced inspections at the premises of manufacturers of active substances used as starting materials, or at the premises of marketing authorisation holders whenever it considers that there are grounds for suspecting non-compliance with the principles and guidelines of good manufacturing practice referred to in Article 47. These inspections may also be carried out at the request of a Member State, the Commission or the Agency.</p> <p>In order to verify whether the data submitted in order to obtain a conformity certificate comply with the monographs of the European Pharmacopoeia, the standardisation body of the nomenclatures and the quality norms within the meaning of the Convention relating to the elaboration of the European Pharmacopoeia ⁵ (European Directorate for the quality of Medicinal Products) may ask the Commission or the Agency to request such an inspection when the starting material concerned is the subject of a European Pharmacopoeia monograph.</p> <p>The competent authority of the Member State concerned may carry out</p>
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⁴ OJ L 158, 25.6.1994, p. 19.

⁵ OJ L 158, 25.6.1994, p. 19.

<p>inspections of starting material manufacturers at the specific request of the manufacturer himself.</p> <p>Such inspections shall be carried out by officials representing the competent authority that shall be empowered to:</p> <p>(a) inspect the manufacturing or commercial establishments of manufacturers of medicinal products or of active substances used as starting materials, and any laboratories employed by the holder of the manufacturing authorisation to carry out checks pursuant to Article 20;</p> <p>(b) take samples including with a view to independent tests being carried out by an Official Medicines Control Laboratory or a laboratory designated for that purpose by a Member State;</p> <p>(c) examine any documents relating to the object of the inspection, subject to the provisions in force in the Member States on 21 May 1975 placing restrictions on these powers with regard to the description of the manufacturing method;</p> <p>(d) inspect the premises, records and documents of marketing authorisation holders or any firms employed by the marketing authorisation holder to perform the activities described in Title IX, and in particular Articles 103 and 104.</p> <p>2. Member States shall take all appropriate steps to ensure that the manufacturing processes used in the manufacture of immunological products are properly validated and attain batch -to-batch consistency.</p> <p>3. After every inspection as referred to in paragraph 1, the officials representing the competent authority shall report on whether the manufacturer complies with the principles and guidelines of good</p>	<p>inspections of starting material manufacturers at the specific request of the manufacturer himself.</p> <p>Such inspections shall be carried out by officials representing the competent authority that shall be empowered to:</p> <p>(a) inspect the manufacturing or commercial establishments of manufacturers of medicinal products or of active substances used as starting materials, and any laboratories employed by the holder of the manufacturing authorisation to carry out checks pursuant to Article 20;</p> <p>(b) take samples including with a view to independent tests being carried out by an Official Medicines Control Laboratory or a laboratory designated for that purpose by a Member State;</p> <p>(c) examine any documents relating to the object of the inspection, subject to the provisions in force in the Member States on 21 May 1975 placing restrictions on these powers with regard to the description of the manufacturing method;</p> <p>(d) inspect the premises, records and documents <u>including the pharmacovigilance system master file</u> of marketing authorisation holders or any firms employed by the marketing authorisation holder to perform the activities described in the <u>pharmacovigilance system master file</u> and Title IX and in particular Articles 103 and 104.</p> <p>2. Member States shall take all appropriate steps to ensure that the manufacturing processes used in the manufacture of immunological products are properly validated and attain batch -to-batch consistency.</p> <p>3. After every inspection as referred to in paragraph 1, the officials representing the competent authority shall report on whether the</p>
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manufacturing practice laid down in Article 47 or, where appropriate, with the requirements laid down in Articles 101 to 108. The content of such reports shall be communicated to the manufacturer or marketing authorisation holder who has undergone the inspection.

4. Without prejudice to any arrangements which may have been concluded between the Community and third countries, a Member State, the Commission or the Agency may require a manufacturer established in a third country to submit to an inspection as referred to in paragraph 1.

5. Within 90 days of an inspection as referred to in paragraph 1, a certificate of good manufacturing practice shall be issued to a manufacturer if the outcome of the inspection shows that the manufacturer complies with the principles and guidelines of good manufacturing practice as provided for by Community legislation.

If inspections are performed as part of the certification procedure for the monographs of the European Pharmacopoeia, a certificate shall be drawn up.

6. Member States shall enter the certificates of good manufacturing practice which they issue in a Community database managed by the Agency on behalf of the Community.

7. If the outcome of the inspection as referred to in 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.

[Regulation (EC) No 726/2004 Article 19]

manufacturer complies with the principles and guidelines of good manufacturing practice laid down in Article 47 or, where appropriate, with the requirements laid down in Articles 101 a to 101p. The content of such reports shall be communicated to the manufacturer or marketing authorisation holder who has undergone the inspection.

4. Without prejudice to any arrangements which may have been concluded between the Community and third countries, a Member State, the Commission or the Agency may require a manufacturer established in a third country to submit to an inspection as referred to in paragraph 1.

5. Within 90 days of an inspection as referred to in paragraph 1, a certificate of good manufacturing practice shall be issued to a manufacturer if the outcome of the inspection shows that the manufacturer complies with the principles and guidelines of good manufacturing practice as provided for by Community legislation.

If inspections are performed as part of the certification procedure for the monographs of the European Pharmacopoeia, a certificate shall be drawn up.

6. Member States shall enter the certificates of good manufacturing practice which they issue in a Community database managed by the Agency on behalf of the Community.

7. If the outcome of the inspection as referred to in 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.

	<p><u>8. The Member States shall send all pharmacovigilance inspection reports to the Agency. 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 master file and Title IX, the Member State competent authority shall inform the other Member States, the Agency and the Commission. The Member State shall bring the deficiencies to the attention of the marketing authorisation holder and where appropriate shall take the necessary measures to ensure that a marketing authorisation holder is subject to effective, proportionate and dissuasive penalties as referred to in Article 101n.</u></p>
<p>Direction 2001/83/EC Article 116</p> <p>The competent authorities shall suspend, revoke, withdraw or vary a marketing authorisation if the view is taken that the product is harmful under normal conditions of use, or that it lacks therapeutic efficacy, or that the risk-benefit balance is not positive under the normal conditions of use, or that its qualitative and quantitative composition is not as declared. Therapeutic efficacy is lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.</p> <p>[Regulation (EC) No 726/2004 Article 20]</p>	<p>Direction 2001/83/EC Article 116</p> <p>The competent authorities shall suspend, revoke, withdraw or vary a marketing authorisation if the view is taken that the product is harmful in normal conditions of use, or that it lacks therapeutic efficacy, or that the risk-benefit balance is not positive under normal conditions of use, or that its qualitative and quantitative composition is not as declared. Therapeutic efficacy is lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.</p>
<p>Direction 2001/83/EC Article 117</p> <p>1. Without prejudice to the measures provided for in Article 116, Member States shall take all appropriate steps to ensure that the supply of the medicinal product is prohibited and the medicinal product withdrawn from the market, if the view is taken that:</p> <p>(a) the medicinal product is harmful under normal conditions of use; or</p> <p>(b) it lacks therapeutic efficacy; or</p> <p>(c) the risk-benefit balance is not favourable under the authorised</p>	<p>Direction 2001/83/EC Article 117</p> <p>1. Without prejudice to the measures provided for in Article 116, Member States shall take all appropriate steps to ensure that the supply of the medicinal product is prohibited and the medicinal product withdrawn from the market, if the view is taken that:</p> <p>(a) the medicinal product is harmful under normal conditions of use; or</p> <p>(b) it lacks therapeutic efficacy; or</p> <p>(a) the risk-benefit balance is not favourable under the authorised</p>

<p>conditions of use; or</p> <p>(d) its qualitative and quantitative composition is not as declared; or</p> <p>(e) the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled.</p> <p>2. The competent authority may limit the prohibition to supply the product, or its withdrawal from the market, to those batches which are the subject of dispute.</p> <p>[Regulation (EC) No 726/2004 Article 20]</p>	<p>conditions of use; or</p> <p>(b) its qualitative and quantitative composition is not as declared; or</p> <p>(c) the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled.</p> <p>2. The competent authority may limit the prohibition to supply the product, or its withdrawal from the market, to those batches which are the subject of dispute.</p> <p><u>3. The competent authority may limit the prohibition to supply the product to new patients.</u></p>
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<p>Direction 2001/83/EC Article 123</p> <p>1. Each Member State shall take all the appropriate measures to ensure that decisions authorizing marketing, refusing or revoking a marketing authorization, cancelling a decision refusing or revoking a marketing authorization, prohibiting supply, or withdrawing a product from the market, together with the reasons on which such decisions are based, are brought to the attention of the Agency forthwith .</p> <p>2. The marketing authorization holder shall be obliged to notify the Member States concerned forthwith of any action taken by him to suspend the marketing of a medicinal product or to withdraw a medicinal product from the market, together with the reasons for such action if the latter concerns the efficacy of the medicinal product or the protection of public health. Member States shall ensure that this information is brought to the attention of the Agency.</p> <p>3. Member States shall ensure that appropriate information about action taken pursuant to paragraphs 1 and 2 which may affect the protection of public health in third countries is forthwith brought to the attention of the World Health Organization, with a copy to the Agency.</p> <p>4. The Commission shall publish annually a list of the medicinal products which are prohibited in the Community.</p>	<p>Direction 2001/83/EC Article 123</p> <p>1. Each Member State shall take all the appropriate measures to ensure that decisions authorizing marketing, refusing or revoking a marketing authorization, cancelling a decision refusing or revoking a marketing authorization, prohibiting supply, or withdrawing a product from the market, together with the reasons on which such decisions are based, are brought to the attention of the Agency forthwith.</p> <p>2. The marketing authorization holder shall be obliged to notify the Member States concerned forthwith of any action taken by him to suspend the marketing of a medicinal product or to withdraw a medicinal product from the market, together with the reasons for such action if the latter concerns the efficacy of the medicinal product or the protection of public health. Member States shall ensure that this information is brought to the attention of the Agency.</p> <p>3. Member States shall ensure that appropriate information about action taken pursuant to paragraphs 1 and 2 which may affect the protection of public health in third countries is forthwith brought to the attention of the World Health Organization, with a copy to the Agency.</p> <p>4. The Commission <u>Agency</u> shall publish annually a list of the medicinal products which are prohibited in the Community.</p>
<p>Direction 2001/83/EC Article 127a</p> <p>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 with regard to the safe and effective use of the medicinal product as provided for in Article 9(4)(c) of that Regulation, a decision addressed to the Member</p>	<p>Direction 2001/83/EC Article 127a</p> <p><u>The Member States shall ensure that laws, procedures and resources are in place to allow enforcement of measures included in risk management plans referred to in Article 22 and the measures referred to in Article 117(3).</u></p>

<p>States shall be adopted in accordance with the procedure provided for in Articles 33 and 34 of this Directive, for the implementation of those conditions or restrictions.</p>	<p>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 with regard to the safe and effective use of the medicinal product as provided for in Article 9(4)(c) of that Regulation, a decision addressed to the Member States shall <u>may</u> be adopted in accordance with the procedure provided for in Articles 33 and 34 of this Directive, for the implementation of those conditions or restrictions.</p>
<p>Regulation (EC) No 726/2004 Article 18</p> <p>1. In the case of medicinal products for human use manufactured within the Community, the supervisory authorities 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.</p> <p>2. In the case of medicinal products imported from third countries, the supervisory authorities 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.</p> <p>A Member State may request assistance from another Member State or from the Agency.</p>	<p>Regulation (EC) No 726/2004 Article 18</p> <p>1. In the case of medicinal products for human use manufactured within the Community, the supervisory authorities 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.</p> <p>2. In the case of medicinal products imported from third countries, the supervisory authorities 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.</p> <p>A Member State may request assistance from another Member State or from the Agency.</p> <p>3. <u>For the purposes of inspection the supervisory authority for</u></p>

	<u>pharmacovigilance shall be the competent authorities of the Member State in which the qualified person responsible for pharmacovigilance resides.</u>
<p>Regulation (EC) No 726/2004 Article 56(1)</p> <p>1. The Agency shall comprise:</p> <p>(a) the Committee for Medicinal Products for Human Use, which shall be responsible for preparing the opinion of the Agency on any question relating to the evaluation of medicinal products for human use;</p>	<p>Regulation (EC) No 726/2004 Article 56(1)</p> <p>1. The Agency shall comprise:</p> <p>(a) the Committee for Medicinal Products for Human Use, which shall be responsible for preparing the opinion of the Agency on any question relating to the evaluation of medicinal products for human use;</p> <p><u>(aa) the Committee on Pharmacovigilance;</u></p>
<p>Regulation (EC) No 726/2004 Article 57(2)</p> <p>2. The database provided for in paragraph 1(l) shall include the summaries of product characteristics, the patient or user package leaflet and the information shown on the labelling. The database shall be developed in stages, priority being given to medicinal products authorised under this Regulation and those authorised under Chapter 4 of Title III of Directive 2001/83/EC and of Directive 2001/82/EC respectively. The database shall subsequently be extended to include any medicinal product placed on the market within the Community.</p> <p>Where appropriate, the database shall also include references to data on clinical trials currently being carried out or already completed, contained in the clinical trials database provided for in Article 11 of Directive 2001/20/EC. The Commission shall, in consultation with the Member States, issue guidelines on data fields which could be included and which may be accessible to the public.</p>	<p>Regulation (EC) No 726/2004 Article 57(2)</p> <p>2. The database provided for in paragraph 1 (l) shall include the summaries of product characteristics, the patient or user package leaflet and the information shown on the labelling. The database shall be developed in stages, priority being given to medicinal products authorised under this Regulation and those authorised under Chapter 4 of Title III of Directive 2001/83/EC and of Directive 2001/82/EC respectively. The database shall subsequently be extended to include any medicinal product placed on the market within the Community.</p> <p><u>For the purposes of this database, the Agency shall establish a list of all medicinal products authorised in the Community. To support this task:</u></p> <p><u>(a) by -/- (six-months after the entry into force of the directive) the Agency shall make public a format for the electronic submission of medicinal product information;</u></p> <p><u>(b) by -/- (eighteen months after the entry into force of the directive)</u></p>

	<p><u>marketing authorisation holders in the Community shall electronically submit to the Agency medicinal product information compliant with the format referred to in point (a) for all medicinal products authorised or registered in the Community.</u></p> <p><u>(c) from the date referred to in point (b) marketing authorisation holders shall notify the Agency of any new authorisations granted in the Community compliant with the format referred to in point (a).</u></p> <p>Where appropriate, the database shall also include references to data on clinical trials currently being carried out or already completed, contained in the clinical trials database provided for in Article 11 of Directive 2001/20/EC. The Commission shall, in consultation with the Member States, issue guidelines on data fields which could be included and which may be accessible to the public.</p>
<p>Regulation (EC) No 726/2004 Article 61(1 and 2)</p> <p>1. Each Member State shall, after consultation of the Management Board, appoint, for a three-year term which may be renewed, one member and one alternate to the Committee for Medicinal Products for Human Use and one member and one alternate to the Committee for Medicinal Products for Veterinary Use.</p> <p>The alternates shall represent and vote for the members in their absence and may act as rapporteurs in accordance with Article 62.</p> <p>Members and alternates shall be chosen for their role and experience in the evaluation of medicinal products for human and veterinary use as appropriate and shall represent the competent national authorities.</p> <p>2. The committees may co-opt a maximum of five additional members chosen on the basis of their specific scientific competence. These members shall be appointed for a term of three years, which may be</p>	<p>Regulation (EC) No 726/2004 Article 61(1 and 2)</p> <p>1. Each Member State shall, after consultation of the Management Board, appoint, for a three-year term which may be renewed, one member and one alternate to the Committee for Medicinal Products for Human Use, and <u>one member and one alternate to the Committee for Medicinal Products for Veterinary Use and one member and one alternate to the Committee on Pharmacovigilance.</u></p> <p>The alternates shall represent and vote for the members in their absence and may act as rapporteurs in accordance with Article 62.</p> <p>Members and alternates shall be chosen for their role and experience in the evaluation of medicinal products for human and veterinary use as appropriate and shall represent the competent national authorities.</p> <p>2. The committees may co-opt a maximum of five additional members chosen on the basis of their specific scientific competence. These</p>

<p>renewed, and shall not have alternates.</p> <p>With a view to the co-opting of such members, the committees shall identify the specific complementary scientific competence of the additional member(s). Co-opted members shall be chosen among experts nominated by Member States or the Agency.</p>	<p>members shall be appointed for a term of three years, which may be renewed, and shall not have alternates.</p> <p>With a view to the co-opting of such members, the committees shall identify the specific complementary scientific competence of the additional member(s). Co-opted members shall be chosen among experts nominated by Member States or the Agency.</p> <p><u>The Pharmacovigilance Committee shall additionally include:</u></p> <p><u>(a) two members and two alternates appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent health professionals;</u></p> <p><u>(b) two members and two alternates appointed by the Commission, on the basis of a public call for expressions of interest, after consulting the European Parliament, in order to represent patient associations.</u></p>
<p>Regulation (EC) No 726/2004 Article 62</p> <p>1. Where, in accordance with the provisions of this Regulation, the Committee for Medicinal Products for Human Use, the Committee on Herbal Medicinal Products or the Committee for Medicinal Products for Veterinary Use 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.</p> <p>When consulting the scientific advisory groups referred to in Article 56(2), the Committee shall forward to them the draft assessment report(s) drawn up by the rapporteur or the co-rapporteur. The opinion issued by the scientific advisory group shall be forwarded to the chairman of the relevant Committee in such a way as to ensure that the</p>	<p>Regulation (EC) No 726/2004 Article 62</p> <p>1. Where, in accordance with the provisions of this Regulation, the Committee for Medicinal Products for Human Use, the Committee on Herbal Medicinal Products, or the Committee for Medicinal Products for Veterinary Use <u>or the Committee on Pharmacovigilance</u> 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.</p> <p>When consulting the scientific advisory groups referred to in Article 56(2), the Committee shall forward to them the draft assessment report(s) drawn up by the rapporteur or the co-rapporteur. The opinion issued by the scientific advisory group shall be forwarded to the chairman of the relevant Committee in such a way as to ensure that the</p>

<p>deadlines laid down in Article 6(3) and Article 31(3) are met.</p> <p>The substance of the opinion shall be included in the assessment report published pursuant to Article 13(3) and Article 38(3).</p> <p>If there is a request for re-examination of one of its opinions, 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 consult a scientific advisory group in connection with the re-examination.</p> <p>2. 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 the Committee for Medicinal Products for Human Use, the Committee on Herbal Medicinal Products or the Committee for Medicinal Products for Veterinary Use, together with an indication of their qualifications and specific areas of expertise.</p> <p>The Agency shall keep an up-to-date list of accredited experts. The list shall include the experts referred to in the first subparagraph and other experts appointed directly by the Agency. The list shall be updated.</p> <p>3. The provision of services by rapporteurs or experts shall be governed by a written contract between the Agency and the person concerned, or where appropriate between the Agency and his employer.</p> <p>The person concerned, or his employer, shall be remunerated in accordance with a scale of fees to be included in the financial</p>	<p>deadlines laid down in Article 6(3) and Article 31(3) are met.</p> <p>The substance of the opinion shall be included in the assessment report published pursuant to Article 13(3) and Article 38(3).</p> <p>If there is a request for re-examination of one of its opinions, 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 consult a scientific advisory group in connection with the re-examination.</p> <p>2. 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 the Committee for Medicinal Products for Human Use, the Committee on Herbal Medicinal Products, or the Committee for Medicinal Products for Veterinary Use <u>or the Committee on Pharmacovigilance</u>, together with an indication of their qualifications and specific areas of expertise.</p> <p>The Agency shall keep an up-to-date list of accredited experts. The list shall include the experts referred to in the first subparagraph and other experts appointed directly by the Agency. The list shall be updated.</p> <p>3. The provision of services by rapporteurs or experts shall be governed by a written contract between the Agency and the person concerned, or where appropriate between the Agency and his employer.</p> <p>The person concerned, or his employer, shall be remunerated in</p>
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<p>arrangements established by the Management Board.</p> <p>4. The performance of scientific services for which there are several potential providers may result in a call for an expression of interest, if the scientific and technical context allows, and if it is compatible with the tasks of the Agency, in particular to ensure a high level of public health protection.</p> <p>The Management Board shall adopt the appropriate procedures on a proposal from the Executive Director.</p> <p>5. The Agency or any of the committees referred to in Article 56(1) may use the services of experts for the discharge of other specific tasks for which they are responsible.</p>	<p>accordance with a scale of fees to be included in the financial arrangements established by the Management Board.</p> <p>4. The performance of scientific services for which there are several potential providers may result in a call for an expression of interest, if the scientific and technical context allows, and if it is compatible with the tasks of the Agency, in particular to ensure a high level of public health protection.</p> <p>The Management Board shall adopt the appropriate procedures on a proposal from the Executive Director.</p> <p>5. The Agency or any of the committees referred to in Article 56(1) may use the services of experts for the discharge of other specific tasks for which they are responsible.</p> <p><u>[Note paragraph 3 will apply to the pharmacovigilance committee and therefore remuneration will be paid based on contracts]</u></p>
<p>Regulation (EC) No 540/95 Commission Regulation (EC) No 540/95 of 10 March 1995 laying down the arrangements for reporting suspected unexpected adverse reactions which are not serious, whether arising in the Community or in a third country, to medicinal products for human or veterinary use authorized in accordance with the provisions of Council Regulation (EEC) No 2309/93 (<i>OJ No L 55 of 11. 3. 1995, p. 5</i>)</p>	<p>[To be repealed by the Commission after the adoption of the new legislation].</p>

ANNEX 2: Table of Correspondence for Title IX of Directive 2001/83/EC

<u>Article in the proposal</u>	<u>Corresponding existing provision, if any</u>
Directive 2001/83/EC, Title IX, Chapter 1 "Reporting of adverse reactions by healthcare professionals and identification of biological medicinal products which are the subject of adverse reaction reports", Article 101a.	Existing text of Article 101 with new provisions relating to the identification of biological medicinal products which are the subject of adverse reaction reports.
Directive 2001/83/EC, Title IX, Chapter 2, "Good Vigilance Practice", Article 101b.	An adaptation and clarification of the existing text of Directive 2001/83/EC Article 106 which is the current legal basis for Volume 9A of Eudralex.
Directive 2001/83/EC, Title IX, Chapter 3, "Independence", Article 101c.	A clarification of the existing text of Directive 2001/83/EC Article 102a.
Directive 2001/83/EC, Title IX, Chapter 4, "Data management and reporting" Section 1 "Eudravigilance and recording and reporting of adverse reactions", Article 101d.	Modification of Directive 2001/83/EC Article 102 and 105, plus new provisions on safety signal detection and public access
Directive 2001/83/EC, Title IX, Chapter 4, "Data management and reporting" Section 1 "Eudravigilance and recording and reporting of adverse reactions", Article 101e.	Modification of Directive 2001/83/EC Article 102, 104, paragraphs 1 to 5, and 105 plus new provisions on medication errors, web-based electronic reporting, monitoring and reporting from the medical literature.
Directive 2001/83/EC, Title IX, Chapter 4, "Data management and reporting" Section 1 "Eudravigilance and recording and reporting of adverse reactions", Article 101f.	Extensive modification of Directive 2001/83/EC Article 104, paragraphs 6 to 8 on Periodic Safety Update Reporting.
Directive 2001/83/EC, Title IX, Chapter 4, "Data management and reporting" Section 2 "Post-authorisation safety studies", Article 101g.	Extension and clarification of the existing provision of Directive 2001/83/EC Article 23 last subparagraph to provide a clearer legal basis for requiring post-authorisation safety studies of authorised medicinal products.
Directive 2001/83/EC, Title IX, Chapter 4, "Data management and reporting" Section 2 "Post-authorisation safety studies", Article 101h.	Procedure for the Competent Authority or the Pharmacovigilance Committee to scrutinise protocols for non-interventional post-authorisation safety studies that involve collection of data. Clarification and simplification of existing provisions in Volume 9A of Eudralex.
Directive 2001/83/EC, Title IX, Chapter 5,	Directive 2001/83/EC Articles 102 second

"Communications", Article 101 i.	subparagraph and 104(9) and provisions from Volume 9A of Euralex plus extensive new transparency and communication provisions.
Directive 2001/83/EC, Title IX, Chapter 5, "Communications", Article 101 j.	New provision on the making public of the intensive monitoring list.
Directive 2001/83/EC, Title IX, Chapter 6, "Community Assessment and binding decisions", Article 101 k.	Clarification of the existing provision of Directive 2001/83/EC Article 107.
Directive 2001/83/EC, Title IX, Chapter 7, "Responsibilities and tasks", Article 101 l.	Certain provisions are based on Directive 2001/83/EC Articles 102, 103, 105 plus provisions in Volume 9A of Euralex
Directive 2001/83/EC, Title IX, Chapter 8, "General provisions", Article 101 m.	Provisions on World Health Organisation liaison are not currently included in Title IX of Directive 2001/83/EC.
Directive 2001/83/EC, Title IX, Chapter 8, "General provisions", Article 101 n.	Provisions on continuous cooperation to develop the system are not currently included in Title IX of Directive 2001/83/EC.
Directive 2001/83/EC, Title IX, Chapter 8, "General provisions", Article 101 o.	Penalties are currently covered in Directive 2001/83/EC Article 104(9) last subparagraph.
Directive 2001/83/EC, Title IX, Chapter 8, "General provisions", Article 101 p.	New transitional measures providing the basis for risk management systems to be required for authorised medicinal products.
Directive 2001/83/EC, Title IX, Chapter 8, "General provisions", Article 101 q.	Clarification of the existing provision of Directive 2001/83/EC Article 108.