OPINION

of the Committee on Industry, Research and Energy

for the Committee on the Environment, Public Health and Food Safety


Rapporteur: Michèle Rivasi
SHORT JUSTIFICATION

These two proposals (a regulation and a directive) on pharmacovigilance place us right at the heart of current issues. The arguments surrounding the vaccine against AH1N1 influenza, which was put on the market following a very quick procedure, illustrate the public's loss of confidence in the ability of the authorities to guarantee their protection. A recent study shows that 61% of French doctors do not intend to have themselves vaccinated. This context further highlights (if it were necessary to do so) the need for the European Union to have an effective pharmacovigilance policy, to reassure and protect its citizens.

We are unfortunately able to point to several cases of medicinal products in recent years which, despite having been placed on the market upon completion of a traditional procedure, have produced substantial side-effects:
- rofecoxib (Vioxx®, Ceox®, Ceeox®): an anti-inflammatory which is no more effective than ibuprofene and which triggered thousands of fatal heart attacks; authorised in 1999 and withdrawn from the market in 2004;
- paroxetine: an anti-depressant (Deroxat®, Seroxat®) which increased the risk of suicide;
- rimonabant (Acomplia®): an anti-obesity medicine, which was put on the market without adequate assessment and withdrawn from the European market a year and a half later.
Several court cases have shown that pharmaceutical companies have a tendency to conceal information about adverse reactions to their medicinal products, which might damage sales, for as long as possible.
In each of these cases we were able to see that the length of the decision-making process and the withholding of information about adverse reactions were harmful to patients.

The human cost of such side-effects is unacceptable; as for the financial costs, these are massive, and it is society as a whole which bears them, because they account for 5% of hospital admissions and 5% of the causes of hospital deaths.

From assessment, via supervision and information relating to medicinal products, to placing them on the market

Before medicinal products are granted marketing authorisation they have to be assessed. This is done over a limited period using a sample of selected patients. Pharmacovigilance's role is subsequently to extend our knowledge of adverse reactions, so as to limit the harm caused to the public.

Your rapporteur fears that the Directive will weaken the pharmacovigilance system, instead of strengthening it, for the reasons given below.

1. The risk management plans and other post-authorisation studies may be used as a backstop in order to reduce assessment before marketing authorisations are granted. This must remain an exception.

2. The ending of the requirement for funding to be public threatens to reduce the pharmacovigilance system to the status of service provider to pharmaceutical firms. The rapporteur proposes, instead, to strengthen the independent national and regional pharmacovigilance systems.
3. Companies' increased control over the collection, analysis and interpretation of the data places them in an untenable situation regarding conflicts of interest. Firms should be able to take part in the study of adverse reactions, but under the control of the authorities, and in no circumstances in a monopoly position.

4. The organisation of dilution of the data, which are stored directly in Eudravigilance, a mega-database, without any procedure to ensure that the quality of the content of Eudravigilance is safeguarded. Your rapporteur proposes that input to Eudravigilance be restricted to the Member States' relevant pharmacovigilance authorities (no direct input by patients, nor by pharmaceutical firms, with the risk of creating too much background noise and thus making the relevant data unusable).

5. The very limited access to the Eudravigilance database for the public and independent experts. Transparency with regard to pharmacovigilance data is essential in order to restore public confidence in the health authorities.

Several proposals are still too cautious and should be strengthened.

1. The formal establishment of a European risk management advisory committee (PRAAC), without any more genuine authority or autonomy than the current Pharmacovigilance Working Party, does not contribute any significant added value.
2. Lack of transparency where pharmacovigilance data is concerned remains the rule: for instance, there is no access to PSURs, on the pretext of commercial confidentiality. PSURs and all assessment reports should be published immediately.

To conclude:

- Strengthen the criteria to enable marketing authorisation to be granted on surer grounds, entailing the requirement for new medicinal products to bring genuine therapeutic advances; no widespread use of the fast-track procedure
- Ensure the quality of pharmacovigilance data
- Provide the resources to ensure effective public pharmacovigilance

**Increase transparency**

**AMENDMENTS**

The Committee on Industry, Research and Energy calls on the Committee on the Environment, Public Health and Food Safety, as the committee responsible, to incorporate the following amendments in its report:

**Amendment 1**

Proposal for a directive – amending act

Recital 5

*Text proposed by the Commission*  
(5) For the sake of clarity, the definition of  

*Amendment*  
(5) For the sake of clarity, the definition of
adverse reaction should be amended to ensure that it not only covers noxious and unintended effects derived from the authorised use of a medicinal product at the normal doses, but also medication errors and uses outside the authorised summary of the product characteristics, including the misuse and abuse of the product.

Justification

The definition of adverse reaction covers all unintended effects derived from misuse, including medication errors. The directive does not, however, aim to give information on medication errors in general, but only on medication errors leading to unintended effects.

Amendment 2

Proposal for a directive – amending act
Recital 7

Text proposed by the Commission

(7) The planning of pharmacovigilance for each individual medicinal product by the marketing authorisation holder should take place in the context of a risk management system and should be proportionate to the identified risks, potential risks, and the need for additional information on the medicinal product. It should also be foreseen that any key measures contained in a risk management system are included in the marketing authorisation as conditions.

Amendment

(7) The planning of pharmacovigilance for each individual medicinal product by the marketing authorisation holder should take place in the context of a risk management system and should be proportionate to the identified risks, potential risks, and the need for additional information on the medicinal product. It should also be foreseen that any key measures contained in a risk management system are included in the marketing authorisation as conditions. If the conditions included in the marketing authorisation are not fulfilled within the corresponding deadline, the competent authorities should have the power and appropriate resources to immediately suspend or revoke the marketing authorisation.

Justification

Experience shows that in many cases where companies were required to conduct post-authorisation safety studies they failed to do so. The result is that doctors and patients remain
unsure whether some critical medicines used to treat illnesses like cancer and heart disease are actually beneficial. That is why it is essential to introduce stricter requirements in the legislation in order to ensure that pharmaceutical companies complete their promised studies.

**Amendment 3**

**Proposal for a directive – amending act**

**Recital 8**

*Text proposed by the Commission*

(8) In order to ensure the collection of any necessary additional data about the safety of authorised medicinal products, competent authorities should be empowered to require post-authorisation safety studies at the time of the granting of the marketing authorisation or later, and this requirement should be included as a condition of the marketing authorisation.

*Amendment*

(8) In order to ensure the collection of any necessary additional data about the safety of authorised medicinal products, competent authorities should be empowered to require post-authorisation safety studies at the time of the granting of the marketing authorisation or later, and this requirement should be included as a condition of the marketing authorisation. If the conditions included in the marketing authorisation are not fulfilled within the deadline set, the competent authorities should have the power and appropriate resources to immediately suspend or revoke the marketing authorisation.

**Justification**

Experience shows that in many cases where companies were required to conduct post-authorisation safety studies they failed to do so. The result is that doctors and patients remain unsure whether some critical medicines used to treat illnesses like cancer and heart disease are actually beneficial. That is why it is essential to introduce stricter requirements in the legislation in order to ensure that pharmaceutical companies complete their promised studies.

**Amendment 4**

**Proposal for a directive – amending act**

**Recital 9**

*Text proposed by the Commission*

(9) Where a medicinal product is authorized subject to the requirement to conduct a post-authorisation safety study or where there are conditions or restrictions with regard to the safe and effective use of the medicinal product, the medicinal product should be intensively monitored on

*Amendment*

(9) Where, in the case of an unmet medical need, a medicinal product is authorized subject to the requirement to conduct a post-authorisation safety study or where there are conditions or restrictions with regard to the safe and effective use of the medicinal product, the medicinal
the market. Patients and healthcare professionals should be encouraged to report all suspect adverse reactions to such medicinal products, and a publicly available list of such medicinal products should be maintained up to date by the European Medicines Agency established by Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (hereinafter referred to as the ‘Agency’).

Justification

Special warnings for intensively monitored medicines will help both the health professionals and the patients to identify new medicines under intensive surveillance and would increase their awareness to report any adverse reaction that might appear as already recommended by the US Institute of Medicine in its 2006 report. This measure could be further improved by adding on the box a pictogram like for example the black triangle ( ) already well known and used in some Member States.

Amendment 5

Proposal for a directive – amending act

Recital 10

Text proposed by the Commission

(10) In order to make it possible for the healthcare professionals and patients to identify easily the most relevant information about the medicines they use, the summary of the product characteristics and the package leaflet should include a concise section on the key information about the medicinal product should be intensively monitored on the market. Steps must be taken to ensure that tightening up the pharmacovigilance system does not result in marketing authorisations being issued prematurely. Patients and healthcare professionals should be encouraged to report all suspect adverse reactions to such medicinal products, which should be identified by a specific symbol on the outer packaging and by a corresponding explanatory sentence in the leaflet, and a publicly available list of such medicinal products should be maintained up to date by the European Medicines Agency established by Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (hereinafter referred to as the ‘Agency’).

Amendment

(10) Within five years of the entry into force of this Directive, the Commission should, following consultations with patient and consumer organisations, healthcare professional organisations, Member States and other interested parties, present to the European Parliament and the Council an
product and information how to minimize its risks and maximize its benefits.

assessment report regarding the readability of the summaries of product characteristics and the packaging leaflets. Following an analysis of such data, the Commission should, if appropriate, put forward proposals to improve the layout and the content of the summaries of product characteristics and of the packaging leaflet to ensure they are a valuable source of information for the general public and healthcare professionals.

Justification

The notion of a summary poses a problem. It is more important for the report to be drawn up legibly to ensure that the patient reads all the necessary information.

Amendment 6

Proposal for a directive – amending act
Recital 17

Text proposed by the Commission

(17) To further increase the coordination of resources between the Member States, Member State should be authorised to delegate certain pharmacovigilance tasks to another Member State.

Amendment

(17) Each Member State should be responsible for the oversight of the adverse reactions occurring in its territory. To further increase the level of expertise in pharmacovigilance, Member States should be encouraged to organise training and to regularly exchange information and expertise.

Justification

Each member state should be fully responsible for the detection and the follow up of any adverse event related to a medicine marketed within its territory.

Amendment 7

Proposal for a directive – amending act
Recital 19

Text proposed by the Commission

(19) In order to increase the level of transparency on the processes of

Amendment

(19) In order to increase the level of transparency on the processes of
pharmacovigilance, the Member States should create and maintain medicines safety web-portals. **To the same end**, the marketing authorisation holders should **provide** the authorities with **prior warning about** safety announcements and the authorities should provide each other with **such a warning**.

**Justification**

*It is important to ensure that any information on medicines provided by companies to the general public is non promotional. The principle of prior validation of the information is already applied for package leaflets, public campaigns and also in the proposal on information to the general public on prescription medicines currently under discussion and for consistency it should be applied to pharmacovigilance information.*

**Amendment 8**

**Proposal for a directive – amending act**

**Recital 28**

*Text proposed by the Commission*

(28) In order to protect public health, there should be adequate funding of activities related to pharmacovigilance by the national competent authorities. **It should be possible to ensure adequate funding for pharmacovigilance activities through the collection of fees. However, the management of those collected funds should be under the permanent control of the national competent authorities in order to guarantee their independence.**

*Amendment*

(28) In order to protect public health, there should be adequate funding of activities related to pharmacovigilance by the national competent authorities.

**Justification**

*Pharmacovigilance activities should be publicly financed not only to ensure their independence but also because the Member States should be fully responsible for pharmacovigilance (also in terms of funding) as they are those who bear the costs associated with side effects both in terms of morbidity and in terms of mortality. According to the European Commission “it is estimated that 5% of all hospital admissions are due to an adverse drug reaction, 5% of all hospital patients suffer an adverse reaction and adverse reactions are the fifth most common cause of hospital death.*
Amendment 9

Proposal for a directive – amending act
Recital 29 a (new)

Text proposed by the Commission

(29a) This Directive should apply without prejudice to Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data¹ and Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data². In order to detect, assess, understand and prevent adverse reactions, identify and take action to reduce the risks and increase the benefits of medicinal products for the purpose of safeguarding public health, it should be possible to process personal data within the Eudravigilance system while complying with EU data protection legislation. That purpose constitutes a substantial public interest which can be justified if identifiable health data are processed only when necessary and the parties involved assess such necessity at every stage of the pharmacovigilance process.

¹ OJ L 281, 23.11.1995, p. 31.

Justification

The proposal covers highly sensitive personal information which should be fully protected. See also opinion of the European data protection supervisor of April 2009.

Amendment 10

Proposal for a directive – amending act
Article 1 – point 1 – point a
Directive 2001/83/EC
Article 1 – point 11
(a) point 11 is replaced by the following: 

`'(11) Adverse reaction: A response to a medicinal product which is noxious and unintended'`

**Justification**

The initial wording (Article 1, point 11, of consolidated Directive 2001/83/EC), which clearly states that it refers to normal conditions of use and avoids confusion with cases involving misuse or abuse, should be reinstated.

**Amendment 11**

**Proposal for a directive – amending act**

**Article 1 – point 1 – point b**

Directive 2001/83/EC

Article 1 – point 14

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Text proposed by the Commission

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

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(14) Suspected adverse drug reaction: An unintended event in respect of which a causal relationship between the event and the medicinal product cannot be excluded.
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**Justification**

The term ‘adverse reaction’ should be replaced by the more precise term ‘adverse drug reaction’, which is used by experts and is internationally accepted. Drafting note: The remaining text of the directive and of Regulation (EC) No 726/2004 will have to be changed accordingly if this amendment is adopted.

**Amendment 12**

**Proposal for a directive – amending act**

**Article 1 – point 1 – point c**

Directive 2001/83/EC

Article 1 – point 15

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Text proposed by the Commission

(15) Post-authorisation safety study: Any study with an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety
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**Amendment**

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(15) Post-authorisation pharmacovigilance study: Any study with a medicinal product authorised early for reasons of public health in the absence of a therapeutic alternative, or carried out at the request of
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profile of the medicinal product, or of measuring the effectiveness of risk management measures.

the health authorities once a medicinal product has been placed on the market, with the aim of identifying, characterising or quantifying an adverse reaction risk or of assessing the adverse reaction profile of the medicinal product and its risk/benefit balance, or of measuring the effectiveness of risk management measures.

Justification

The aim of a post-authorisation study is to monitor the adverse reactions of medicinal products in human beings. It is not intended to monitor ‘post-authorisation safety’. Post-authorisation safety studies must not be used to obtain marketing authorisations on the cheap, without sufficient evaluation.

Amendment 13

Proposal for a directive – amending act
Article 1 – point 1 – point d
Directive 2001/83/EC
Article 1 – point 28b

Text proposed by the Commission

(28b) Risk management system: a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to a medicinal product, including the assessment of the effectiveness of those interventions.

Amendment

(28b) Risk management system: a set of specific pharmacovigilance activities and interventions designed to quantify or prevent risks already detected, and risks identified subsequently, relating to a medicinal product, including the assessment of the effectiveness of those interventions, or to ensure early identification of new risks.

Justification

All medicinal products available on the European market must be seriously monitored by the general pharmacovigilance system, which needs to be made more effective both at European and national levels. The aim of a risk management system should not be to ‘identify the risks of a medicinal product’: that is the role of the pre-marketing authorisation assessment. A risk management system should make it possible to prevent risks already identified thanks to the pre-marketing authorisation assessment.
Amendment 14

Proposal for a directive – amending act
Article 1 – point 1 – point d
Directive 2001/83/EC
Article 1 – point 28c

Text proposed by the Commission

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

Amendment

(28c) Pharmacovigilance system: a system allowing marketing authorisation holders and Member States, with a view to fulfilling the tasks and responsibilities listed in Title IX:

(a) to collect information useful in the surveillance of medicinal products, with particular reference to adverse reactions in human beings, including misuse and abuse of medicinal products and medication errors; and

(b) to evaluate such information scientifically in order to detect any change to the risk-benefit balance of authorised medicinal products.

Justification

Pharmacovigilance is an observational scientific discipline first and foremost for the benefit of patients. It is not designed to monitor the ‘safety of medicinal products’ (an ambiguous expression whose vocabulary is misleading because of its positive connotation): pharmacovigilance data are not commercial data collected by companies as part of their after-sales service. The aim of pharmacovigilance is to monitor the adverse reactions of medicinal products in human beings.

Amendment 15

Proposal for a directive – amending act
Article 1 – point 1 – point d a (new)
Directive 2001/83/EC
Article 1 – points 32 a, 32 b and 32 c (new)

Text proposed by the Commission

(da) The following points are inserted:

Amendment

(da) The following points are inserted:
‘(32a) Medication error: a non-intentional omission or action relating to a medicinal product which can be the cause of a risk or of an adverse event for the patient. A medication error is by definition preventable because it evidences what should have been done and what was not done during the patient’s medicinal therapy. A medication error can concern one or more stages in the medicinal product’s cycle, such as formulary selection, prescription, dispensing, validation, preparation, storage, delivery, administration and therapeutic monitoring and information, but also its interfaces, such as communications and transcriptions.

(32b) Misuse: use, of a medicinal product, that is not in compliance with the recommendations in the summary of the product characteristics.

(32c) Medically justified use not in accordance with indications: specific case of use deliberately not in compliance with the recommendations under the ‘indications’ section of the summary of the product characteristics but based on the assessment data.’

Amendment 16
Proposal for a directive – amending act
Article 1 - point 3 - point a
Directive 2001/83/EC
Article 11 – point 3a

Text proposed by the Commission

(a) the following point 3a is inserted:

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

Amendment 17
Proposal for a directive – amending act
Article 1 – point 3 – point b
Directive 2001/83/EC
Article 11 - subparagraph 3

Text proposed by the Commission

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

Amendment

For medicinal products included on the list referred to in Article 23 of Regulation (EC) No 726/2004, the summary shall include the following:

(a) a statement reading "This newly authorised medicinal product is under intensive monitoring in order to increase knowledge of its adverse reactions. All suspected adverse reactions should be reported to <name, web-address, postal address and telephone number of the national competent authority>, or reported directly to the pharmacy.”;

(b) an exclamation mark surrounded by a red triangle. This symbol shall also appear on the outer packaging, accompanied by an indication that it is advisable to read the package leaflet before taking the medicinal product.

Justification

Informar que o medicamento está sob fiscalização intensiva, dada a sua introdução recente no mercado, serve para prevenir alarmismos injustificados que induzam o doente a não cumprir a medicação prescrita. A sinalética escolhida para alertar os doentes deve ter um significado comummente reconhecido pelo público, pelo que alguns sistemas usados nalguns países entre a comunidade médica podem ser desprovidos de sentido para o doente. Para aumentar a frequência de notificação de reacções adversas pelos doentes, convém torná-la fácil de concretizar, por meios informáticos e não informáticos.

Amendment 18

Proposal for a directive – amending act
Article 1 — point 7
Directive 2001/83/EC
Article 21 – paragraph 4 – subparagraph 1
4. The national competent authorities shall draw up an assessment report and comments on the file as regards the results of the pharmaceutical and pre-clinical tests, the clinical trials and the risk management system and the pharmacovigilance system of the medicinal product concerned. The assessment report shall be updated whenever new information becomes available which is of importance for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

Amendment 19

Proposal for a directive – amending act
Article 1 — point 8
Directive 2001/83/EC
Article 21a

Text proposed by the Commission

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

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

Amendment

If the medicinal product responds to unmet medical needs and if its risk-benefit balance may be considered positive, a marketing authorisation may be granted subject to one or more of the following conditions:

(1) to take certain measures for the safe use of the medicinal product contained in the risk management system;
(2) to conduct post-authorisation safety studies;
(3) to comply with requirements on adverse reaction recording or reporting which are stricter than those referred to in Title IX;
(4) any other conditions or restrictions with regard to the safe and effective use of the medicinal product.
The marketing authorisation shall lay down deadlines for the fulfilment of the conditions where necessary. The competent authorities shall have the power and appropriate resources to immediately suspend or revoke the marketing authorisation, where the conditions included in that marketing authorisation are not fulfilled by the relevant deadline.

**Justification**

This amendment is to align the text with the provisions currently in force (Regulation 507/2006) whereby a centralised conditional marketing authorisation may be granted only if the risk benefit balance is positive, the benefit to public health outweighs the risks inherent in the fact that additional data are required and that unmet medical needs will be fulfilled. At the moment, the conditional marketing authorisations must be reassessed annually and in the package leaflet there is a reference specifying that the renewal of the marketing authorisation is linked to the fulfilment of the established conditions.

**Amendment 20**

Proposal for a directive – amending act
Article 1 — point 11
Directive 2001/83/EC
Article 23 – paragraph 4 – subparagraph 1

**Text proposed by the Commission**

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

**Amendment**

4. In order that the risk-benefit balance may be continuously assessed, the national competent authority may at any time ask the holder of the marketing authorisation and its pharmacovigilance system to forward the data necessary for a reassessment of the risk-benefit balance.

**Amendment 21**

Proposal for a directive – amending act
Article 1 – point 14 – point a
Directive 2001/83/EC
Article 27 – paragraph 1
1. **A coordination group** shall be set up **for the following purposes:**

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

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

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

For the fulfilment of its tasks, the coordination group for mutual recognition and decentralised procedures shall be assisted by the Committee for Medicinal Products for Human Use referred to in Article 5(1) of Regulation (EC) No 726/2004.

1. **Two coordination groups** shall be set up:

(a) A coordination group for mutual recognition and decentralised procedures shall be responsible for the following tasks:

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

(ii) the examination of questions related to the pharmacovigilance of medicinal products authorised by the Member States, in accordance with Articles 107c, 107e, 107g, 107l and 107r, for all questions relating to pharmacovigilance.

For the fulfilment of its tasks, the coordination group for mutual recognition and decentralised procedures shall be assisted by the Committee for Medicinal Products for Human Use referred to in Article 5(1) of Regulation (EC) No 726/2004.

(b) A coordination group for pharmacovigilance risk assessment shall be responsible for the following tasks:

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

ii) the examination of questions related to the variations to the terms of marketing authorisations granted by the Member States, in accordance with Article 35(1), for all questions relating to pharmacovigilance.
The Agency shall provide the secretariat of this coordination group.

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

Amendment 22

Proposal for a directive – amending act
Article 1 – point 14 – point a
Directive 2001/83/EC
Article 27 – paragraph 1 – subparagraph 3

Text proposed by the Commission

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

Amendment

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

Justification

Horizontal Change Required throughout Proposal - The proposal establishes a European Pharmacovigilance Risk assessment advisory committee and entrusts it with important pharmacovigilance tasks but with a mere advisory role and no authority - the committee's role should be strengthened and that is to be reflected in its title.

Amendment 23

Proposal for a directive – amending act
Article 1 – point 14 – point b
Directive 2001/83/EC
Article 27 – paragraph 2 - subparagraphs 2 and 3

Text proposed by the Commission

Members of the coordination group and

Amendment

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

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

Amendment 24

Proposal for a directive – amending act
Article 1 – point 18 – point a
Directive 2001/83/EC
Article 59 – paragraph 1 – point aa

Text proposed by the Commission

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

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

Amendment 25

Proposal for a directive – amending act
Article 1 – point 18 – point a a (new)
Directive 2001/83/EC
Article 59 – paragraph 1 – point h a (new)
(aa) the following point (ha) is inserted:

“(ha) a detachable portion of the leaflet that the patient can tear off, including the following statement: “Suspected adverse reactions should be reported to your doctor, pharmacist, or to <name, web-address, postal address and/or telephone and fax number of the national competent authority>.”;”

Amendment 26

Proposal for a directive – amending act
Article 1 – point 18 – point b
Directive 2001/83/EC
Article 59 – paragraph 1 – subparagraphs 2 and 3

Text proposed by the Commission

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

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

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

Justification

As the information in package leaflets are often updated several times per year (2/3 times on average) highlighting the new information in bold and with a special symbol runs the risk of giving patients a wrong impression that this information is the more important information as well as provide a confusing leaflet.
Amendment 27

Proposal for a directive – amending act
Article 1 – point 18 – point b
Directive 2001/83/EC
Article 59 – paragraph 1 – subparagraph 3

Text proposed by the Commission

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

Amendment

For medicinal products included on the list referred to in Article 23 of Regulation (EC) No 726/2004, the following additional elements shall be included:

(a) a statement reading “This newly authorised medicinal product is under intensive monitoring in order to increase knowledge of its adverse reactions. All suspected adverse reactions should be reported to <name, web-address, postal address and telephone number of the national competent authority>, or reported directly to the pharmacy.”;

(b) an exclamation mark surrounded by a red triangle. This symbol shall also appear on the outer packaging, accompanied by an indication that it is advisable to read the package leaflet before taking the medicinal product.

Justification

Informar que o medicamento está sob fiscalização intensiva dada a sua introdução recente no mercado serve para prevenir alarmismos injustificados que induzam o doente a não cumprir a medicação prescrita. A sinalética escolhida para alertar os doentes deve ter um significado comummente reconhecido pelo público, pelo que alguns sistemas usados nalguns países entre a comunidade médica podem ser desprovidos de sentido para o doente. Para aumentar a frequência de notificação de reacções adversas pelos doentes, convém torná-la fácil de concretizar, por meios informáticos e não informáticos.
Amendment 28
Proposal for a directive – amending act
Article 1 — point 20
Directive 2001/83/EC
Article 65 - point g

Text proposed by the Commission

Amendment

20. In Article 65, the following point (g) is added:
“(g) the summary of the essential information necessary to use the medicine safely and effectively provided for in Article 11(3a) and Article 59(1)(aa).”

Amendment 29
Proposal for a directive – amending act
Article 1 — point 21
Directive 2001/83/EC
Article 102

Text proposed by the Commission

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

Amendment

The Member States shall:
(1) take all appropriate measures to encourage patients, doctors, pharmacists and other health-care professionals to report suspected adverse reactions to the national competent authority. Those measures shall include training for healthcare professionals and for patients, and a public information campaign for patients. Patient organisations should be involved in providing information and training to patients;

(1a) conduct public awareness campaigns on the importance of reporting adverse reactions and possible ways of doing so;

(1b) facilitate direct patient reporting, in addition to web-based formats, through the provision on the patient information leaflet of a detachable portion that can be reported to the doctors, pharmacists or the national competent authority;
(2) ensure that adverse reaction reports contain the highest quality information possible;

(3) through the methods of collecting information and where necessary through the follow up of adverse reaction reports, ensure that any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of an adverse reaction report is identifiable;

(2) ensure that adverse reaction reports and the databases contain the highest quality information possible;

(3) ensure that any biological medicinal product prescribed, dispensed, or sold in their territory which is the subject of a suspected adverse reaction report is identifiable by, as far as available, the name of the marketing authorisation holder, the International Non-proprietary Name (INN), the name of the medicinal product and the batch number, using the standard forms and procedures developed in accordance with Article 25 of Regulation (EC) No 726/2004, taking due account of the developments within the EudraVigilance system; and implement the necessary measures to ensure the traceability of biological medicinal products dispensed to patients;

(3a) ensure that the public is given important information in good time on pharmacovigilance concerns relating to the use of a medicinal product and that data is permanently accessible to the public;

(3b) take the necessary steps to enable the public to report adverse reactions, in particular by ensuring that appropriate forms are available at pharmacies, drawn up in line with technical criteria and complying with the principles of simplified language and structure, accessible to the general public; these forms shall be sent by the pharmacists to the competent authorities;

(4) take the necessary measures to ensure that a marketing authorisation holder who fails to discharge the obligations laid down in this Title is subject to effective, proportionate and dissuasive penalties.

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

Justification

It is more appropriate to encourage patients & health professionals to submit their reports to the competent authorities rather than to pharmaceutical companies. Direct reporting to companies raises concerns both in terms of privacy of users and in terms of medical feedback. In addition they will be in the position to decide if the report is an “adverse reaction”, a medication error, or else. Patient reporting should be accompanied by information campaigns about the importance of reporting.

Amendment 30

Proposal for a directive – amending act
Article 1 — point 21
Directive 2001/83/EC
Article 103

Text proposed by the Commission

Amendment

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

The delegating Member State shall inform the Commission, the Agency and all other Member States of the delegation in writing. The delegating Member State and the Agency shall make that information public.

Justification

Each member state should be fully responsible for the detection and the follow up of any adverse event related to a medicine marketed within its territory.

Amendment 31

Proposal for a directive – amending act
Article 1 – point 21
Directive 2001/83/EC
Article 105 – paragraph 2

Text proposed by the Commission

Amendment

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

Amendment 32

Proposal for a directive – amending act
Article 1 — point 21
Directive 2001/83/EC
Article 106

Text proposed by the Commission

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

1. risk management systems for medicinal products authorised in accordance with this Directive;
2. the list of medicinal products under intensive monitoring referred to in Article 23 of Regulation (EC) No 726/2004;

Amendment

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

- (1) the leaflets for the medicines available on the national market in the national language (and where applicable the link to the EMEA EudraPharm database);
- (2) the list of medicinal products under intensive monitoring referred to in Article 23 of Regulation (EC) No 726/2004;
- (3) web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and patients based on the forms referred to in Article 25 of Regulation (EC) No 726/2004;
- (4) agendas for meetings of the Pharmacovigilance Committee and of the coordination group and records of their meetings, accompanied by the decisions taken and by details and explanations of the votes, including minority opinions;
- (5) requests from the national competent authority to the marketing authorisation holder to operate a risk management
system or to conduct a post-authorisation study, together with the explanations provided by the marketing authorisation holder to the national competent authority where necessary, and the final decision of the competent authority.

Justification

Each member state should have a national medicine agency portal to provide high quality information on medicines to the general public. Most countries already have such a portal as a source of validated and reliable information on medicines and this amendments aims at establishing the legal basis for such portals in response to the European Commission report on current practice with regard to the provision of information to patients on medicinal products. The web portal should include a dedicated area for all information related to safety issues and pharmacovigilance.

Amendment 33

Proposal for a directive – amending act
Article 1 — point 21
Directive 2001/83/EC
Article 107

Text proposed by the Commission

1. Marketing authorisation holders shall be required to record all suspected adverse reactions in the Community or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals or occurring in the context of a post-authorisation safety study.

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

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

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

Amendment

1. Marketing authorisation holders shall be required to record all suspected adverse reactions in the Community or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals or occurring in the context of a clinical trial or a post-authorisation safety study.

Suspected adverse reactions occurring in the context of a clinical trial shall also be recorded and reported in accordance with Directive 2001/20/EC.

2. The marketing authorisation holder shall forward to the national competent authorities any reports of suspected adverse reactions received from patients and health-care professionals within 7 days.
of receiving the reports. The marketing authorization holder shall inform the patient and healthcare professional that their report has been forwarded to the competent authorities who will be in charge of following it up. The national competent authorities may not refuse any reports of suspected adverse reactions received by post, telephone, facsimile transmission or in electronic format from patients and healthcare professionals.

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

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

For medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004, marketing authorisation holders shall not be required to report to the Eudravigilance database the suspected adverse reactions recorded in the listed medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions.

For medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004, marketing authorisation holders shall not be required to report to the Eudravigilance database the suspected adverse reactions recorded in the listed medical literature, but they shall monitor all other medical literature and report any suspected adverse reactions.
4. Member States shall access reports on adverse reactions through the Eudravigilance database and shall assess the quality of the data received from marketing authorisation holders. They shall, as appropriate, involve patients and health-care professionals in the follow up of any reports they receive and request follow up of such reports to be conducted by the marketing authorisation holders. The marketing authorisation holders shall be required to report any follow up information received to the Eudravigilance database.

Amendment 34


Text proposed by the Commission

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

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

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

Amendment

1. The Member States shall record all suspected adverse reactions that occur in their territory which are brought to their attention by healthcare professionals, patients, marketing authorisation holders and programmes for the reporting and prevention of medication errors.

Member States shall ensure that reports of such reactions can be submitted by means of the national medicines safety web-portals, as well as by post, telephone and fax.

2. Member States shall, within 15 days following the receipt of the reports referred to in paragraph 1, submit electronically to the database and data-processing network referred to in Article 24 of Regulation (EC) No 726/2004 (hereinafter referred to as ‘the Eudravigilance database’) information on all adverse reactions that occur within their territory within 15 days following receipt of the report or, in the...
Marketing authorisation holders shall access those reports through the Eudravigilance database.

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

Amendment 35

Proposal for a directive – amending act
Article 1 – point 21
Directive 2001/83/EC
Article 107a – paragraph 3 a (new)

Text proposed by the Commission

3a. The Member States shall ensure that marketing authorisation holders may electronically transmit information on unintended effects of medicinal products to national databases so that country-specific safety problems can be identified more effectively and more promptly.
Amendment 36

Proposal for a directive – amending act
Article 1 – point 21
Directive 2001/83/EC
Article 107i – paragraph 1 – points a, b, c

Text proposed by the Commission

(a) it considers suspending or revoking of a marketing authorisation;

(b) it considers prohibiting the supply of a medicinal product;

(c) it considers refusing the renewal of a marketing authorisation;

Amendment

(a) it considers, as a result of the evaluation of pharmacovigilance data:
- suspending or revoking of a marketing authorisation;
- prohibiting the supply of a medicinal product;
- refusing the renewal of a marketing authorisation;

Justification

Clarification of the Community procedure

Amendment 37

Proposal for a directive – amending act
Article 1 – point 21
Directive 2001/83/EC
Article 107k – paragraph 1 – subparagraph 1

Text proposed by the Commission

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

Amendment

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

Amendment 38

Proposal for a directive – amending act
Article 1 — point 21
Directive 2001/83/EC
Article 108
Following consultation with the Agency, Member States and interested parties, the Commission shall adopt and make public guidelines on good pharmacovigilance practice for medicinal products authorised in accordance with Article 6(1) in the following areas:

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

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

For the purposes of Article 102(3) and this Article, the Commission, in cooperation with the Agency, Member States, and stakeholders, shall prepare detailed guidelines on good record-keeping practices for pharmacies and others that dispense or administer medicinal products, to ensure retention of records required in the event of needing to file a pharmacovigilance report or to provide information required by a marketing authorisation holder conducting an evaluation of an adverse event, and to facilitate follow-up investigations by the marketing authorisation holder and national competent authorities.

Justification

The need to comply with the standards of the international conference on harmonisation strengthens the conceptual and technical dependence of the healthcare authorities on pharmaceutical laboratories. Good European pharmacovigilance practice would influence the organisation of the European pharmacovigilance system. That good practice must be drawn up openly, by means of a transparent consultation process based on the needs of European patients and from a scientific perspective.

Amendment 39

Proposal for a directive – amending act

Article 2 – paragraph 1

Text proposed by the Commission

1. With regard to the requirement for the inclusion of a summary of the essential information necessary to use the medicine safely and effectively in the summary of the product characteristics and the package leaflet provided for in point 3a of Article 11 and in point (aa) of Article 59(1) of Directive 2001/83/EC as amended by this Directive, the Member States shall ensure that the requirement applies to a marketing authorisation granted before the date set out in the second subparagraph of Article 3(1) of this Directive from renewal of that...

Amendment

1. With regard to the requirement for the inclusion of the medicinal product's adverse reaction profile in the summary of the product characteristics and the package leaflet provided for in point 3a of Article 11 and in point (aa) of Article 59(1) of Directive 2001/83/EC as amended by this Directive, the Member States shall ensure that the requirement applies to a marketing authorisation granted before the date set out in the second subparagraph of Article 3(1) of this Directive from renewal of that authorisation or from the expiry of a period of three years starting from that date,
authorisation or from the expiry of a period of three years starting from that date, whichever is the earliest.
## PROCEDURE

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<td>19.10.2009</td>
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<td>Date appointed</td>
<td>Michèle Rivasi</td>
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<tr>
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<td>16.9.2009</td>
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<td>Members present for the final vote</td>
<td>Jean-Pierre Audy, Zigmantas Balčytis, Bendt Bendtsen, Jan Březina, Maria Da Graça Carvalho, Giles Chichester, Pilar del Castillo Vera, Lena Ek, Ioan Enciu, Adam Gierek, Norbert Glante, Robert Goebbels, Fiona Hall, Jacky Hénin, Edit Herczog, Oriol Junqueras Vies, Sajjad Karim, Arturs Krišjānis Kariņš, Bogdan Kazimierz Marcinkiewicz, Marisa Matias, Judith A. Merkies, Jaroslav Paška, Aldo Patriciello, Miloslav Ransdorf, Herbert Reul, Michèle Rivasi, Jens Rohde, Paul Rübig, Amalia Sartori, Francisco Sosa Wagner, Konrad Szymański, Silvia-Adriana Țicău, Patrizia Toia, Evžen Tošenovský, Ioannis A. Tsoukalas, Claude Turmes, Niki Tzavela, Vladimir Urutchev, Adina-Ioana Vălean, Kathleen Van Brempt, Alejo Vidal-Quadras</td>
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<tr>
<td>Substitute(s) present for the final vote</td>
<td>Lara Comi, António Fernando Correia De Campos, Rachida Dati, Françoise Grossetête, Jolanta Emilia Hibner, Bernd Lange, Marian-Jean Marinescu, Ivari Padar, Vladko Todorov Panayotov, Mario Pirillo</td>
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<tr>
<td>Substitute(s) under Rule 187(2) present for the final vote</td>
<td>Isabelle Durant</td>
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