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Committee on the Environment, Public Health and Food Safety

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DRAFT REPORT

on the proposal for a directive of the European Parliament and of the Council amending Directive 2001/83/EC as regards pharmacovigilance (COM(2012)0052 – C7-0033/2012 – 2012/0025(COD))

Committee on the Environment, Public Health and Food Safety

Rapporteur: Linda McAvan

Symbols for procedures

- * Consultation procedure
- *** Consent procedure
- ***I Ordinary legislative procedure (first reading)
- ***II Ordinary legislative procedure (second reading)
- ***III Ordinary legislative procedure (third reading)

(The type of procedure depends on the legal basis proposed by the draft act.)

Amendments to a draft act

In amendments by Parliament, amendments to draft acts are highlighted in ***bold italics***. Highlighting in *normal italics* is an indication for the relevant departments showing parts of the draft act which may require correction when the final text is prepared – for instance, obvious errors or omissions in a language version. Suggested corrections of this kind are subject to the agreement of the departments concerned.

The heading for any amendment to an existing act that the draft act seeks to amend includes a third line identifying the existing act and a fourth line identifying the provision in that act that Parliament wishes to amend. Passages in an existing act that Parliament wishes to amend, but that the draft act has left unchanged, are highlighted in **bold**. Any deletions that Parliament wishes to make in such passages are indicated thus: [...].

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DRAFT EUROPEAN PARLIAMENT LEGISLATIVE RESOLUTION

on the proposal for a directive of the European Parliament and of the Council amending Directive 2001/83/EC as regards pharmacovigilance (COM(2012)0052 – C7-0033/2012 – 2012/0025(COD))

(Ordinary legislative procedure: first reading)

The European Parliament,

- having regard to the Commission proposal to Parliament and the Council (COM(2012)0052),
 - having regard to Article 294(2) and Article 114 and Article 168(4)(c) of the Treaty on the Functioning of the European Union, pursuant to which the Commission submitted the proposal to Parliament (C7-0034/2012),
 - having regard to Article 294(3) of the Treaty on the Functioning of the European Union,
 - having regard to Rule 55 of its Rules of Procedure,
 - having regard to the report of the Committee on the Environment, Public Health and Food Safety A7-0000/2012,
1. Adopts its position at first reading hereinafter set out;
 2. Calls on the Commission to refer the matter to Parliament again if it intends to amend the proposal substantially or replace it with another text;
 3. Instructs its President to forward its position to the Council, the Commission and the national parliaments.

Amendment 1

Proposal for a directive

Recital 2

Text proposed by the Commission

(2) In addition, voluntary action by the marketing authorisation holder should not lead to a situation where concerns related to the risks or benefits of a medicinal product authorised in the Union are not properly addressed in all Member States. Therefore, provisions should be made for the marketing authorisation holder to inform competent authorities of the reasons

Amendment

(2) In addition, voluntary action by the marketing authorisation holder should not lead to a situation where concerns related to the risks or benefits of a medicinal product authorised in the Union are not properly addressed in all Member States. Therefore, provisions should be made for the marketing authorisation holder to inform competent authorities *and the*

for the withdrawal of a medicinal product, for interrupting the placing on the market of a medicinal product, for requests for revoking a marketing authorisation, or for not renewing a marketing authorisation.

Agency of the reasons for the withdrawal of a medicinal product, for interrupting the placing on the market of a medicinal product, for requests for revoking a marketing authorisation, or for not renewing a marketing authorisation.

Or. en

Amendment 2

Proposal for a directive

Article 1 - point 2

Directive 2001/83/EC

Article 31 – paragraph 1 – subparagraph 3 a (new) and 3 b (new)

Text proposed by the Commission

Amendment

The Member State concerned or the Commission shall clearly identify the question which is referred to the Committee for consideration and shall inform the applicant or marketing authorisation holder accordingly.

The Member States and the applicant or marketing authorisation holder shall supply the Committee with all available information relating to the matter in question.

Or. en

Justification

It is useful to reinsert these two obligations which make the Article 31 referral procedure work more smoothly. This text was deleted in the Commission's proposal.

Amendment 3

Proposal for a directive

Article 1 - point 5

Directive 2001/83/EC

Article 123 - paragraph 2

Text proposed by the Commission

2. The marketing authorization holder shall be obliged to notify Member States forthwith of any action taken by him to suspend the marketing of a medicinal product, to withdraw a medicinal product from the market, to request the withdrawal of a marketing authorisation or not to apply for the renewal of a marketing authorisation, together with the reasons for such action. The marketing authorisation holder shall in particular declare if such action is linked to any of the grounds set out in Articles 116 and 117. ***In such case, Member States shall ensure that this information is brought to the attention of the Agency.***

Amendment

2. The marketing authorization holder shall be obliged to notify Member States ***and the Agency*** forthwith of any action taken by him to suspend the marketing of a medicinal product, to withdraw a medicinal product from the market, to request the withdrawal of a marketing authorisation or not to apply for the renewal of a marketing authorisation, together with the reasons for such action. The marketing authorisation holder shall in particular declare if such action is linked to any of the grounds set out in Articles 116 and 117.

Or. en

Justification

The Agency should be notified of all withdrawals / non renewals etc., not just those actions linked to safety or efficacy concerns, i.e. the grounds set out in Articles 116 and 117.

Amendment 4

Proposal for a directive

Article 1 - point 5

Directive 2001/83/EC

Article 123 - paragraph 2 a (new)

Text proposed by the Commission

Amendment

2a. The marketing authorisation holder shall also make the notification pursuant to paragraph 2 if the action is taken in a third country and such action is based on

any of the grounds set out in Article 116 and Article 117(1).

Or. en

Justification

It would be useful for regulators to know if a company withdraws / does not renew etc. a marketing authorisation in a third country.

Amendment 5

Proposal for a directive

Article 1 - point 5 a

Directive 2001/83/EC

Article 123 - paragraph 4

Text proposed by the Commission

Amendment

(5a) Article 123(4) is replaced by the following:

4. The Agency shall make public annually a list of the medicinal products for which marketing authorisations have been refused, revoked or suspended, whose supply has been prohibited or which have been withdrawn from the market, including the reasons for such action.

Or. en

Justification

In the interests of transparency the Agency should not just publish the list of products which have been withdrawn etc. but should also state the reasons for such action. They are already given this information.

EXPLANATORY STATEMENT

Background to the Revision

In December 2010, the European Parliament and the Council agreed a revision of the rules governing pharmacovigilance at EU level by adopting Directive 2010/84/EU and Regulation 1235/2010. This new legislation is due to apply in July 2012. The rapporteur believes that the range of measures adopted in this new legislation will lead to improved safety of medicines at EU level by strengthening the role of the European Medicines Agency (EMA) in collecting and acting on signal detection and increasing cooperation between Member States.

However, the emergence of a major medicine safety enquiry in France, the “Mediator” case in 2011 (see below) prompted calls for an urgent review of pharmacovigilance systems in the EU. The European Commission responded by carrying a “stress test” on the December 2010 legislation in order to identify any additional lessons which needed to be learned in the light of the Mediator case. The result of the stress tests showed that while the new legislation did strengthen pharmacovigilance at EU level, there are some potential weaknesses in the EU system that needs to be addressed. The Commission is therefore proposing some further changes to Directive 2010/84/EU and Regulation 1235/2010 to address these concerns.

Your rapporteur hopes that, in the interests of public health, Council and Parliament can reach agreement on these changes in first reading so that any changes can be incorporated into law before the planned implementation date of July 2012. In order to reach rapid agreement, the rapporteur wishes to concentrate on amendments arising from the lessons learned from the Mediator case and not to reopen other issues. She is grateful for the cooperation of shadow rapporteurs on this matter.

The Mediator Case in France

Mediator was a medicine made by the French company Servier and licensed in a number of EU countries through national procedures (France, Portugal, Luxembourg, Greece, Italy and Spain) for the treatment of type 2 diabetes. Its main active ingredient was benfluorex and as far back as 1998, there were first ADR (Adverse Reaction) reports indicating concerns about possible heart valve disorders. In both the USA and the EU, similar anorectic agents - dexfenfluramine and fenfluramine - were taken off the market in the late 1990s.

Despite this, Mediator was widely prescribed in Europe and in particular France. By 2009 when the drug was finally withdrawn from the market, an estimated 5m people had been prescribed the medicine and it was one of the top 50 most prescribed medicines in the world. Evidence suggests it had also been prescribed more widely than for diabetics as a general appetite suppressant. Estimates of the number of deaths related to Mediator vary from five hundred to two thousand.

A note prepared by the European Medicines Agency in January 2011 shows that concerns about Mediator and its active ingredient Benfluorex were discussed by regulators at various meetings at European level over a period of years going as far back as 1998. In 2000, an

assessment by the Italian authorities recommended that the Marketing Authorisation Holder (MAH) undertake a study to examine these concerns, but according to a report of the French Senate, though the protocol for the study was agreed in February 2001, the study was not started until 2006 and not completed until 2009. In fact, despite all these well documented concerns, no decision was taken to refer Mediator to the then Committee for Human Medicinal Products (CHMP) for a formal scientific assessment at EU level, meaning that no further action was taken by regulators. In 2003 the company, Servier, let its marketing licence for benfluorex lapse in both Spain and Italy, but under the current rules, a decision not to reapply for a licence does not trigger any investigatory action. Servier claimed the withdrawal was for commercial reasons and Member States were simply informed of the decision via the European Medicine Agency's (EMA) regular "Drug Monitor" publication. It was only in November 2009 when fresh evidence was brought to light in France and France suspended the marketing authorization that Mediator was finally referred to the CHMP and its marketing authorization in the EU withdrawn.

There are several criminal investigations into Mediator ongoing in France, including one by a public prosecutor who is investigating Servier for deception and involuntary manslaughter.

Commission proposed changes to the existing pharmacovigilance legislation in response to Mediator

The Commission's stress tests suggest that though much improves under the new system, further changes are needed to close any potential loopholes.

- **An automatic urgent procedure** (article 107i, Directive) The 2010 legislation already specifies a list of triggers which would activate the urgency procedure (e.g. if a Member State withdraws a drug), but Member States have some discretion over this. The Commission is now proposing to make the urgent procedure purely automatic.
- **A new trigger for the urgent procedure** (article 107i, Directive) If companies decide not to apply to renew a marketing licence due to safety reasons (as was the case for Mediator), then this should trigger the urgent procedure.
- **Clarification of transparency obligations on companies** (article 123(2), Directive) When companies voluntarily withdraw a drug or do not reapply for a marketing licence they must specifically declare if this is due to a safety concern. (When Servier did not reapply for authorisation for Mediator in Italy and Spain, they claimed it was for commercial reasons.)
- **A longer list of medicines subject to additional monitoring** (article 23, Regulation) The list of "black symbol" drugs subject to additional monitoring should systematically include all drugs subject to some kind of post-authorisation safety study (PASS), or certain other conditions or requirements. In the 2010 legislation, the Commission originally proposed that any drug subject to outstanding conditions should be classified in this way. The concept of "additional monitoring" is an important tool to encourage the "informed" patient and greater awareness among healthcare professionals about the need to look out for and report ADRs. It can also act as a driver for companies to complete post authorisation studies. However, during

negotiations this automatic requirement was removed and an element of discretion introduced so that the authorities could add these drugs on a case-by-case basis. As mentioned above, Mediator was subject to a PASS which was not completed until 2009, 8 years after the study protocol was agreed.

Additional amendments from your rapporteur

Your rapporteur agrees with the general thrust of the Commission proposals which further strengthen the pharmacovigilance system at EU level. The five additional amendments which are proposed and which are explained in full detail under each article serve to clarify wording, ensure that the workload of the PRAC (Pharmacovigilance Risk Assessment Committee) remains manageable and to ensure that patients and healthcare professionals are fully involved in pharmacovigilance.