EUROPEAN PARLIAMENT 2009 - 2014

*Plenary sitting*

**A7-0164/2012**

12.7.2012

# ***I
# REPORT

on the proposal for a regulation of the European Parliament and of the Council amending Regulation (EC) No 726/2004 as regards pharmacovigilance (COM(2012)0051 – C7-0034/2012 – 2012/0023(COD))

Committee on the Environment, Public Health and Food Safety

Rapporteur: Linda McAvan

PR_COD_1amCom

***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: **[...]**.

**CONTENTS**

**Page**

## DRAFT EUROPEAN PARLIAMENT LEGISLATIVE RESOLUTION

**on the proposal for a regulation of the European Parliament and of the Council amending Regulation (EC) No 726/2004 as regards pharmacovigilance (COM(2012)0051 – C7-0034/2012 – 2012/0023(COD))**

**(Ordinary legislative procedure: first reading)**

*The European Parliament*,

– having regard to the Commission proposal to Parliament and the Council (COM(2012)0051),

– 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 (A7-0164/2012),

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 regulation**
**Recital 1**

| *Text proposed by the Commission* | *Amendment* |
|---|---|
| (1) In order to ensure transparency on the surveillance of authorised medicinal products, the list of medicinal products subject to additional monitoring 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 | (1) In order to ensure transparency on the surveillance of authorised medicinal products, the list of medicinal products subject to additional monitoring 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, as amended by Regulation (EU) No 1235/2010, should systematically include medicinal products that are subject to post-authorisation safety conditions. | products for human and veterinary use and establishing a European Medicines Agency, as amended by Regulation (EU) No 1235/2010, should systematically include medicinal products that are subject to ***certain*** post-authorisation safety conditions. |

**Amendment 2**

**Proposal for a regulation**
**Article 1 - point 4**
Regulation (EC) No 726/2004
Article 23 – paragraph 1 – points c and d

| *Text proposed by the Commission* | *Amendment* |
|---|---|
| (c) medicinal products that are authorised pursuant to this Regulation subject to conditions referred to in points ***(c), (ca),*** (cb) and (cc) of Article 9(4), or in Article 10a***,*** Article 14(7) and (8) ***and in Article 21(2)***; | (c) medicinal products that are authorised pursuant to this Regulation subject to conditions referred to in points (cb) and (cc) of Article 9(4), or in Article 10a ***and*** Article 14(7) and (8); |
| (d) medicinal products that are authorised pursuant to Directive 2001/83/EC, subject to the conditions referred to in ***Articles*** 21a, 22, 22a ***and 104a*** of that Directive; | (d) medicinal products that are authorised pursuant to Directive 2001/83/EC, subject to the conditions referred to in ***points (b), (c) and (f) of Article*** 21a, ***or in Articles*** 22, ***and*** 22a of that Directive; |

*Justification*

*The list of products subject to additional monitoring should only include products subject to the most serious conditions and safety concerns, as otherwise the list becomes too long and loses meaning.*

*It should automatically include all new products containing new active substances, as well as all new biosimilars, for the first five years. It should also automatically include any products subject to:*

- *a PASS (as was the case for Mediator)*[1]*;*
- *a PAES*[2]*;*
- *stricter-than-normal rules on ADR reporting*[3]*;*
- *a "conditional market authorisation" (i.e. for unmet medical need)* [4]

[1] Regulation articles 9(4)cb and 10a, and Directive articles 21a(b) and 22a
[2] Regulation articles 9(4)cc and 10a, and Directive articles 21a(f) and 22a
[3] Regulation article 9(4)cb and Directive article 21a(c)
[4] Regulation article 14(7)

- *an "exceptional market authorisation" (i.e. for orphan diseases)*[1]

*Products subject to any other conditions should only be included at the discretion of Member States and the Commission, after consultation of the PRAC.*

**Amendment 3**

**Proposal for a regulation**
**Article 1 - point 4**
Regulation (EC) No 726/2004
Article 23 – paragraph 1 a (new)

| *Text proposed by the Commission* | *Amendment* |
|---|---|
| | ***1a. At the request of the Commission, following consultation with the Pharmacovigilance Risk Assessment Committee, medicinal products that are authorised pursuant to this Regulation may, subject to conditions referred to in points (c) and (ca) of Article 9(4) and in Article 21(2), also be included in the list.*** |
| | ***At the request of a national competent authority, following consultation with the Pharmacovigilance Risk Assessment Committee, medicinal products that are authorised pursuant to Directive 2001/83/EC may, subject to the conditions referred to in points (d) and (e) of Article 21a, and Article 104a of that Directive, also be included in the list.*** |

*Justification*

*The list of products subject to additional monitoring should only include products subject to the most serious conditions and safety concerns, as otherwise the list becomes too long and loses meaning.*
*It should automatically include all new products containing new active substances, as well as all new biosimilars, for the first five years. It should also automatically include any products subject to:*

- *a PASS (as was the case for Mediator)*[2]*;*
- *a PAES*[3]*;*
- *stricter-than-normal rules on ADR reporting*[4]*;*

[1] Regulation article 14(8) and Directive article 22
[2] Regulation articles 9(4)cb and 10a, and Directive articles 21a(b) and 22a
[3] Regulation articles 9(4)cc and 10a, and Directive articles 21a(f) and 22a
[4] Regulation article 9(4)cb and Directive article 21a(c)

- *a "conditional market authorisation" (i.e. for unmet medical need)* [1]
- *an "exceptional market authorisation" (i.e. for orphan diseases)*[2]

*Products subject to any other conditions should only be included at the discretion of Member States and the Commission, after consultation of the PRAC.*

**Amendment 4**

**Proposal for a regulation**
**Article 1 - point 4**
Regulation (EC) No 726/2004
Article 23 – paragraph 4

| *Text proposed by the Commission* | *Amendment* |
|---|---|
| 4. For medicinal products included in that list, the summary of product characteristics and the package leaflet shall include the statement "This medicinal product is subject to additional monitoring". That statement shall be preceded by a black symbol which shall be selected by the Commission following a recommendation of the Pharmacovigilance Risk Assessment Committee by ***2 January 2012***, and shall be followed by an appropriate standardised explanatory sentence. | 4. For medicinal products included in that list, the summary of product characteristics and the package leaflet shall include the statement "This medicinal product is subject to additional monitoring". That statement shall be preceded by a black symbol which shall be selected by the Commission following a recommendation of the Pharmacovigilance Risk Assessment Committee by ***2 July 2013***, and shall be followed by an appropriate standardised explanatory sentence. |

*Justification*

*This amendment corrects a drafting mistake in the current legislation. The PRAC is not constituted until July 2012, and so the 12 month deadline should start from then.*

**Amendment 5**

**Proposal for a regulation**
**Article 1 - point 4 a (new)**
Regulation (EC) No 726/2004
Article 67 - paragraph 3 - subparagraph 2 a (new)

| *Text proposed by the Commission* | *Amendment* |
|---|---|
| | ***(4a) In Article 67(3) the following*** |

[1] Regulation article 14(7)
[2] Regulation article 14(8) and Directive article 22

***subparagraphs are added:***

***"By way of derogation from Article 70(1), fees that are required for services provided by the Agency as regards activities relating to pharmacovigilance and by the coordination group as regards the fulfilment of its tasks referred to in the first subparagraph shall be specified by the Commission.***

***For this purpose the Commission shall, after consultation with the Agency, adopt by means of delegated acts, in accordance with Article 87ba, and subject to the conditions of Articles 87c and 87d, measures supplementing the third subparagraph as regards the structure and the level of those fees.".***

*Justification*

*In order to ensure full implementation of the new provisions related to pharmacovigilance, it is urgent to empower the European Medicines Agency to charge fees to marketing authorisation holders for the fulfilment of the pharmacovigilance tasks. Consequently, the Commission should be empowered to adopt a delegated act in accordance with Article 290 TFEU in order to supplement the provisions in Article 67(3) as regards services provided by the Agency or the coordination group with respect to pharmacovigilance.*

**Amendment 6**

**Proposal for a regulation**
**Article 1 - point 4 b (new)**
Regulation (EC) No 726/2004
Article 87b – paragraph 1 a (new)

| *Text proposed by the Commission* | *Amendment* |
|---|---|
| | ***(4b) In Article 87b, the following paragraph is inserted:*** |
| | ***"1a. The power to adopt the delegated acts referred to in Article 67(3) shall be conferred on the Commission for a period of 5 years from 1 July 2012. The Commission shall draw up a report in respect of the delegated powers not later than 6 months before the end of the 5 year period. The delegation of powers shall be*** |

***automatically extended for periods of an identical duration, unless the European Parliament or the Council revokes it in accordance with Article 87c.".***

**Amendment 7**

**Proposal for a regulation**
**Article 1 - point 4 c (new)**
Regulation (EC) No 726/2004
Article 87c - paragraph 1

| *Text proposed by the Commission* | *Amendment* |
|---|---|
| | ***(4c) Article 87c(1) is replaced by the following:*** |
| | **"1. The delegation of powers referred to in Article 10b *and Article 67(3)* may be revoked at any time by the European Parliament or by the Council.".** |

## EXPLANATORY STATEMENT

### Background to the Revision

In December 2010, the European Parliament and the Council agreed a revision of the rules governing pharmacovilgilance 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 need 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 licenced 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 1999, there was a 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 France. 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 pharmovigilance 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 (as it was the case for Mediator), and if this is due to safety reasons, 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 four 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.

**Legislative footprint: Proposals for a Regulation and a Directive of the European Parliament and of the Council concerning Pharmacovigilance of medicinal products for human use.**

As Rapporteur for the European Parliament's Reports on Pharmacovigilance, Linda McAvan met with, received, or heard from representatives from the following organisations and bodies:

| **Industry** |
|---|
| |
| European Generic Medicines Association (EGA) |
| European Federation of Pharmaceutical Industries and Associations (EFPIA) |
| EuropaBio |
| Reckitt Benckiser |
| British Chamber of Commerce |
| Novartis |
| Sanofi-Aventis |
| Sandoz International |
| Servier |
| Astro Zeneka |
| Sidley Austin |
| Teva |
| |
| **Patient, Professional or Consumer Groups** |
| |
| European Patients' Forum |
| The European Consumer's Association (BEUC) |
| Pharmacy Group of the European Union (PGEU) |
| Prescrire and International Society of Drug Bulletins (ISDB) |
| Medicines in Europe Forum |
| EU Public Health Alliance (EPHA) |
| |
| **EU and National Regulatory Agencies** |
| |
| European Medicines Agency (EMA) |
| UK Permanent Representative to the EU, and the UK Medicines and Healthcare Regulatory Agency (MHRA) |
| Belgian Permanent Representative to the EU, and Federal Agency for Medicines and Health Products |

**Legislative footprint: 2012 Proposals for a Regulation and a Directive of the European Parliament and of the Council concerning Pharmacovigilance of medicinal products for human use.**

As Rapporteur for the European Parliament's Reports on Pharmacovigilance, Linda McAvan met with, received, or heard from representatives from the following organisations and bodies:

| **EU and National Regulatory Agencies** |
|---|
| |
| European Medicines Agency (EMA) |
| European Commission |
| Danish Permanent Representation to the EU, and Danish Agency for Medicines and Health Products |

## PROCEDURE

| | |
|---|---|
| **Title** | Amendment of Regulation (EC) No 726/2004 as regards pharmacovigilance |
| **References** | COM(2012)0051 – C7-0034/2012 – 2012/0023(COD) |
| **Date submitted to Parliament** | 10.2.2012 |
| **Committee responsible**<br>Date announced in plenary | ENVI<br>16.2.2012 |
| **Committee(s) asked for opinion(s)**<br>Date announced in plenary | ITRE IMCO<br>16.2.2012 16.2.2012 |
| **Not delivering opinions**<br>Date of decision | ITRE IMCO<br>27.2.2012 29.2.2012 |
| **Rapporteur(s)**<br>Date appointed | Linda McAvan<br>20.12.2011 |
| **Discussed in committee** | 22.3.2012 26.4.2012 |
| **Date adopted** | 8.5.2012 |
| **Result of final vote** | +: 50<br>–: 0<br>0: 0 |
| **Members present for the final vote** | Elena Oana Antonescu, Kriton Arsenis, Sophie Auconie, Pilar Ayuso, Paolo Bartolozzi, Lajos Bokros, Martin Callanan, Nessa Childers, Chris Davies, Esther de Lange, Anne Delvaux, Bas Eickhout, Edite Estrela, Karl-Heinz Florenz, Elisabetta Gardini, Matthias Groote, Françoise Grossetête, Cristina Gutiérrez-Cortines, Satu Hassi, Jolanta Emilia Hibner, Karin Kadenbach, Christa Klaß, Jo Leinen, Peter Liese, Kartika Tamara Liotard, Linda McAvan, Radvilė Morkūnaitė-Mikulėnienė, Vladko Todorov Panayotov, Antonyia Parvanova, Andres Perello Rodriguez, Mario Pirillo, Pavel Poc, Anna Rosbach, Oreste Rossi, Dagmar Roth-Behrendt, Richard Seeber, Anja Weisgerber, Åsa Westlund, Glenis Willmott, Marina Yannakoudakis |
| **Substitute(s) present for the final vote** | Margrete Auken, Nikos Chrysogelos, João Ferreira, Filip Kaczmarek, Toine Manders, Alojz Peterle, Christel Schaldemose, Marita Ulvskog, Vladimir Urutchev, Andrea Zanoni |
| **Date tabled** | 12.7.2012 |