AMENDMENTS TO THE PHARMACOVIGILANCE SYSTEM

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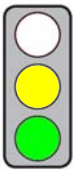
KEY ISSUES

Objective of the Directive and Regulation: The Commission wishes to improve the rules relating to the surveillance of medicinal products ("pharmacovigilance") effective as of 1 July 2012.

Parties affected: Patients, pharmaceutical companies, physicians, pharmacists.



Pros: (1) Expanding the catalogue of medicinal products which are to be automatically included in the list of medicinal products subjected to "additional" surveillance facilitates surveillance and thus improves patient protection.

(2) The new transparency and information obligations for authorisation holders and the automatic initiation of the urgent union procedure also improve patient protection, as the risks in medicinal products can be detected more easily.

Cons: Only those medicinal products should automatically be added to the list which are associated with considerable safety concerns.

CONTENT

Title

Proposal COM(2012) 51 of 10 February 2012 for a **Regulation** of the European Parliament and of the Council amending Regulation (EC) No. 726/2004 as regards pharmacovigilance.
Proposal COM(2012) 52 of 10 February 2012 for a **Directive** of the European Parliament and of the Council amending Directive 2001/83/EC as regards pharmacovigilance.

Brief Summary

Hint: The articles quoted refer to the Regulation No. 726/2004 (REG) and the Directive 2001/83/EC (DIR) to be amended.

- **Background**
  - A pharmacovigilance system is the total set of rules and measures to be applied by marketing authorisation holders and by Member States in order to (DIR Art. 1 No. 28d):
    - collate information on the health risks of medicinal products;
    - monitor the safety of authorised medicinal products and any changes to their risk-benefit balance.
  - On 15 December 2010, the "2010 pharmacovigilance legislation" (Regulation (EU) No. 1235/2010 and Directive 2010/84/EU) were adopted amending Regulation (EC) No. 726/2004 and the Directive 2001/83/EC taking effect on 1 July 2012.
  - Now the Commission intends to revise the pharmacovigilance rules of 2010 in order to eliminate shortcomings in the EU pharmacovigilance system (REG p. 2).
  - The trigger for this was the drug "Mediator". It is suspected of being responsible for 500 to 2,000 deaths in France alone. In Spain, the manufacturer took the drug off from the market in 2003 for commercial reasons but did not have it checked. In France the official authorisation for Mediator was withdrawn in 2009 due to proven considerable side effects.

- **Patient safety: pharmacovigilance and the list of drugs for "additional" surveillance**
  - Basically, each drug is monitored under a risk management system which comprises general measures to minimise risks. Additionally, special measures to minimise risks can be prescribed (DIR Art. 21 (1) in conjunction with DIR Art. 9 (4) lit. c, ca, cb and cc, Art. 10a, Art. 14 (7) and (8) and Art. 21 (2) and/or REG Art. 104 (3) lit. c and d in conjunction with REG Art. 21a, 22, 22a and 104a). Special measures are for instance:
    - safety studies (REG Art. 9 (4) lit. c, cb and REG Art. 21a (1) lit. b),
    - efficacy studies (DIR Art. 9.(4) lit. c, cc and REG Art. 21a (1) lit. f) and
    - requirements as regards informing the authorities of incidents (REG Art. 14 (8)).
  - The European Medicines Agency (EMA) regularly updates a public list of medicinal products which are to undergo additional monitoring (REG Art. 23 (1) sub-para. 1). The purpose of the list is to inform patients as to any particular danger associated with a medicinal product.

Authors: Klaus-Dieter Sohn and Sebastian Czuratis | sohn@cep.eu
CEP | Kaiser-Joseph-Straße 266 | 79098 Freiburg | Germany | Telephone +49 (0)761 38693-105 | www.cep.eu

– According to the current legal position the following medicinal products must be included in the list:
  - automatically: all medicinal products containing a new substance which on 1 January 2011 was not authorised in Member States (REG Art. 23 (1) sub-para. 2 lit. a);
  - automatically: all biological medicinal products authorised after 1 January 2011 (REG Art. 23 (1) sub-para. 2 lit. b);
  - at the discretion of the Commission (in the case of EU-wide authorisation) or the competent national authority (in the case of national authorisation): medicinal products subjected to risk-minimising measures (REG Art. 23 (2));
– In future the list is to also comprise all medicinal products subjected to special measures to minimise risks. The existing rules regarding the discretionary powers of the Commission and the national authorities thereby becomes redundant and will be no longer applicable. (REG new Art. 23 (1) sub-para. 2 lit. c and d)

► **Reporting obligations of authorisation holders**
– To date, the holder of an authorisation must:
  - upon authorisation by EMA (REG Art. 13 (4)) or upon authorisation by a national authority (DIR Art. 123 (2)) inform EMA or all national authorities where
    - the placing on the market of a medicinal product is suspended or
    - a medicinal product is removed from the market;
  - justify the measure if the efficacy of the medicinal product or the protection of the public health is affected.
– In future, the holder of an authorisation must:
  - upon authorisation by EMA (REG amended Art. 13 (4) sub-para. 2 and new Art. 14b) or upon authorisation by national authorities (DIR amended Art. 23a sub-para. 2 and Art. 123 (2)) inform EMA and all national authorities where:
    - the placing on the market of a medicinal product is suspended,
    - a medicinal product is removed from the market,
    - the revocation of an authorisation has been applied for, or
    - the renewal of an authorisation was not applied for;
  - and declare with each notice whether the required measure is taken because (REG new Art. 14b and DIR amended Art. 123 (2), each in conjunction with DIR Art. 116 and 117)
    - the medicinal product is harmful,
    - there is no therapeutic efficacy,
    - the risk-benefit balance is bad,
    - the composition of the medicinal product in terms of type and quantity is not as declared,
    - a medicinal product and its ingredients or intermediate products have not been checked, or
    - other requirements for production authorisation have not been met.

► **Automatic initiation of an urgent union procedure**
– The urgent union procedure (DIR Art. 107i to 107k) is a safety evaluation carried out at EU level by the EMA.
– It is applied to cases:
  - where the Commission or a Member State is considering (DIR Art. 107i (1) lit. a-c)
    - suspending or revoking an authorisation,
    - prohibiting the supply of a medicinal product, or
    - refusing the renewal of an authorisation.
  - The authorisation holder (DIR Art. 107i (1) lit. d and e):
    - informs the Member State that the placing on the market was interrupted due to safety concerns or that he does not wish to renew or return authorisation; or
    - includes a new contraindication, reduces the recommended dosage or restricts indications.
– To date, it is at the discretion of the Commission (in the case of EMA authorisations) or a Member State (in the case of national authorisation) whether or not to carry out an urgent union procedure. Decisive for executing discretion is that "urgent action is considered necessary" by the Commission or Member State as a result of pharmacovigilance data evaluation. (DIR Art. 107i (1)).
– In future, the urgent union procedure is to be initiated automatically in the statutorily required cases (DIR amended Art. 107i (1)).

Statement on Subsidiarity by the Commission

Only EU action may change an EU legal act.

Legislative Procedure

10 February 2012	Adoption by Commission
Open	Adoption by the European Parliament and the Council, publication in the Official Journal of the European Union, entry into force

Options for Influencing the Political Process

Leading Directorate General:	DG Health and Consumers
Committees of the European Parliament:	Environment, Public Health and Food Safety (leading), Rapporteur: Linda McAvan (S&D Group, UK); Industry, Research and Energy; Internal Market
Committees of the German Bundestag:	Health (leading)
Decision mode in the Council:	Qualified majority (approval by a majority of Member States and at least 255 out of 345 votes; Germany: 29 votes)

Formalities

Legal competence:	Art. 114 TFEU (Internal Market)
Form of legislative competence:	Shared competency (Art. 4 (2) TFEU)
Legislative procedure:	Art. 294 TFEU (ordinary legislative procedure)

ASSESSMENT

Economic Impact Assessment

Ordoliberal Assessment

Pharmacovigilance finds itself caught between the pharmaceutical manufacturers' wish to have their new medicinal products authorised as soon as possible and the aims of medicinal product safety, which urges not to issue authorisation until all risks emanating from a medicinal product are certain. A list of medicinal products which are to undergo strengthened surveillance would serve to address this conflict of interests.

Extending the catalogue of medicinal products which are to be automatically subjected to "strengthened" surveillance can help improve surveillance and thus improve **patient protection**. However, **automatic entry into the list should only apply to medicinal products associated with considerable safety concerns** as regards patients. For the blanket extension proposed by the Commission to include all medicinal products subjected to measures minimising risks could lead to increased uncertainty among patients and to the list losing importance in general. For instance, it is not necessary for patients to know details about the requirements for notifying authorities of incidents in order to improve patient safety.

The new transparency and information requirements for authorisation holders do not burden these holders excessively and **improve** the chances for EMA and **the** national authorities **to detect risks in medicinal products**. Moreover, these obligations serve as a basis for the proposed automatic initiation of the urgent union procedure.

Cancelling the discretionary powers of Member States in the case of urgent union procedures can help prevent incidents like the French medicinal product "Mediator" from happening. **The automatic initiation of the urgent union procedure improves patient protection as risks can be detected more easily**. However, this automatism will create increased demands for personnel and finances at EMA if the new tasks are to be adequately processed.

Impact on Efficiency and Individual Freedom of Choice

The strengthening of EMA, which goes hand-in-hand with extending the medicinal product list and the automatism of the urgent union procedure, allows for greater efficiency in the surveillance of medicinal product safety.

Impact on Growth and Employment

Insignificant.

Impact on Europe as a Business Location

As the requirements for authorising medicinal products are not being tightened too significantly, the EU is not expected to a fall behind in terms of the global competition of pharmaceutical research sites.

Legal Assessment

Legislative Competency

Although the proposed measures serve primarily to protect health in the first place, they should also ensure the free movement of goods within the EU. Therefore, the relating competency is laid down in Art. 114 TFEU (cp. ECJ, C-380/03, Germany vs. Parliament and Council – tobacco advertising, No. 40).

Subsidiarity

In accordance with the principle of subsidiarity, the surveillance of medicinal products authorised only in one Member State should really be the responsibility of the Member State concerned, because there is no cross-border relevance. In other words, if a Member State's discretionary powers as to whether or not to carry out an urgent union procedure are reduced to zero, the evaluation would have to be carried out by the national authorisation authority and not by EMA. However, concentrating all the expertise for an evaluation at one

central body serves to ensure a consistently high level of protection in the interest of all patients. It is therefore appropriate.

Proportionality

The proposed measures are in line with the principle of proportionality. For medicinal products can cause considerable harm to the health and life of patients. The automatic updating of the list of medicinal products subjected to strengthened surveillance, the obligation to inform the authorities of as to why an authorisation has been withdrawn and the automatic initiation of an urgent union procedure, in particular where an authorisation is suspended, revoked or not renewed and when withdrawing a medicinal product, are appropriate measures to improve patient protection. The measures do not go beyond what it necessary.

Compatibility with EU Law

Unproblematic.

Compatibility with German Law

Unproblematic.

Alternative Action

Not evident.

Possible Follow-Up EU Action

Not evident.

Conclusion

Extending the catalogue of medicinal products to be automatically included in the list of medicinal products subjected to "strengthened" surveillance facilitates surveillance and thus improves patient protection. However, only medicinal products associated with considerable safety concerns should automatically be added to the list. The new transparency and information obligations for authorisation holders and the automatic initiation of the urgent union procedure also improve patient protection, as risks in medicinal products can be detected more easily.