EU Amendment Directive

PHARMACOVIGILANCE

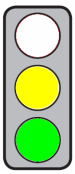
Status: 27.04.09

Centrum für Europäische Politik

MAIN ISSUES

Objective of the Directive: The monitoring of authorised medicinal products is to be reinforced.

Parties Affected: Pharmaceutical manufacturers, patients, national and European authorities.



Pros: The proposed amendments – in particular the establishment of risk management systems for new medicinal products and the extended scope of powers to set post-authorisation requirements – allow for an earlier detection of adverse reactions and thus improve the safety of medicinal products.

Cons: (1) Recording adverse reactions occurring due to incorrect use and placing "essential information" first in the package leaflet are to be rejected.
(2) The EU should not decide on medicinal products authorised in one Member State only.

CONTENT

Title

Proposal COM(2008) 665 of 10 December 2008 for a Directive of the European Parliament and of the Council amending, as regards **pharmacovigilance**, Directive 2001/83/EEC on the Community code relating to medicinal products for human use

Brief Summary

Unless otherwise provided for, the legal provisions cited refer to the Directive 2001/83/EEC to be amended.

- **Basic Terms**
  - A pharmacovigilance system is a set of rules and measures to be applied by marketing authorisation holders ("authorisation") on the one hand and by Member States on the other hand to collect information on the health risks of medicinal products, to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance (new Art. 1 No. 28c; amended Art. 101 and 104).
  - Pharmacovigilance systems must, above all, comprise all actual and all suspected adverse effects of medicinal products.
    - An adverse reaction means "a response to a medicinal product which is noxious and unintended" (amended Art. 1 No. 11), irrespective of whether such a response occurs with correct use within the terms of the marketing authorisation or due to incorrect use of the medicinal product (such as overdose, misuse, abuse and medication errors) (amended Art. 101 (1)).
    - Suspected adverse reaction means "an adverse reaction in respect of which a casual relationship between the event and the medicinal product cannot be excluded" (new Art. 1 No. 14)
    - Pharmacovigilance systems are also to include adverse reactions occurring in the course of studies with the medicinal product or after occupational exposure (amended Art. 101 (1)).
  - Pharmacovigilance systems must enable Member States to "evaluate all information scientifically, consider options for risk minimisation and prevention and take regulatory action as necessary" (amended Art. 101 (2), 104 (2)).
- **Risk management systems as an authorisation requirement for new medicinal products**
  - Medicinal products may – according to their application – be either authorised through national authorities, or – following a vote by the European Medicines Agency (EMEA) – through the Commission. The authorisation requirements are the same in both cases (Art. 6 (1) of the Directive (EC) No. 726/2004).
  - To ensure the appropriate monitoring of medicinal products after authorisation, the following documents must be submitted in both authorisation procedures:
    - A detailed description of the risk management system which the applicant will use; it must serve the detection, description, prevention and minimisation of risks and be in relation to the detected and to the potential risks (new Art. 8 (3) lit. aa, Art. 1 No. 28);
    - A summary of the pharmacovigilance system applied (amended Art. 8 (3) lit. ia), in the scope of which the applicant will appoint a person responsible and maintain a "pharmacovigilance system master file" for the medicinal product concerned (amended Art. 104).
  - Medicinal product authorisations can be granted in particular subject to the condition that its holder
    - accomplishes certain safety studies monitored by the competent authorities,
    - meets certain obligations as regards the recording and reporting of adverse reactions and
    - adjusts its risk management system (amended Art. 22 (1), new Art. 22a).
  - If a medicinal product has been authorised before the Amendment Directive has taken effect, the competent national authority may require the introduction of a risk management system only if there are "concerns" about the risk-benefit balance of the pertaining medicinal product. (new Art. 104a (2)).
- **Package leaflet**
  Package leaflets must include a summary of "the essential information necessary for using the medicine safely and effectively" and highlight it particularly (amended Art. 59 (1)).

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- **Recording and reporting of adverse effects**
  - Marketing authorisation holders must record all suspected adverse reactions in the Community or in third countries and report them to a database of the European Medicines Agency (EMEA) (new Art. 107 (1)).
  - Member States must provide forms on national web-portals for the reporting of adverse reactions by patients and healthcare professionals (new Art. 106) and ensure that reports by healthcare professionals are of "highest quality" (amended Art. 102 (2)).
  - Marketing authorisation holders must submit any suspected adverse reaction electronically within 90 days of receipt; "serious" adverse reactions must be submitted within 15 days (new Art. 107 (3)). Member States must submit any reports within 15 days of receipt (new Art. 107 (2)).
- **Periodic safety update reports of medicinal products**
  - Marketing authorisation holders must submit to EMEA periodic safety update reports on medicinal products marketed by them (new Art. 107b (1)). For various medicinal products containing the same active substance, a Community reference date for the submission may be determined (new Art. 107c (3)).
  - Medicinal products that are subject to a simplified authorisation procedure may be exempted from this obligation (new Art. 107b (3)). This includes generic, homeopathic and traditional herbal medicinal products (Art. 10, 14 and 16a), medicinal products whose active substances have been used in the Community for at least ten years (Art. 10a) and medicinal products whose active substances are identical with active substances of authorised products, but not hitherto used in the same composition (Art. 10b).
- **Assessment of periodic safety update reports**
  - On the basis of periodic safety update reports, it is assessed whether there are new or changed risks and whether the risk-benefit balance has changed:
    - If a medicinal product is authorised in only one Member State, the competent national authority is to assess it (new Art. 107d).
    - If a medicinal product is authorised in more than one Member State or if it belongs to a group of medicinal products for which a Community reference date has been fixed, a "coordination group" composed of national experts is to decide which Member State is in charge of assessing the periodic safety update report concerned (Art. 27 (1), new Art. 107e (1) lit. a). The "coordination group" will be assisted by the "Pharmacovigilance Risk Assessment Advisory Committee" to be newly established by EMEA (amended Art. 56 (1) lit. aa of the Regulation (EC) No. 726/2004).
    - If a medicinal product is subject to EU authorisation, the periodic safety update report is to be assessed by a rapporteur, who is to be appointed by the EMEA Advisory Committee (new Art. 107e (1) lit. b).
  - The assessment reports of the coordination group and of the rapporteur are to be "adopted" by the EMEA Advisory Committee (new Art. 107e (3)).
  - Where medicinal products are authorised in more than one Member State, the assessment procedure is followed by an expert opinion procedure. In the case of medicinal products authorised in only one Member State, a Community procedure is to follow.
- **Expert opinion procedure for medicinal products authorised in more than one Member State**
  - For medicinal products authorised in more than one Member State, the coordination group will provide an expert opinion of the assessment report, adopt a decision by consensus as to which concrete measures to be taken and give the national authorities a deadline for implementation. Where a unanimous decision cannot be made, the Commission is to make it. (new Art. 107g (1) and (2))
  - For medicinal products with EU authorisation, the EMEA Committee for Medicinal Products for Human Use is to adopt an expert opinion on the assessment report and to propose the necessary measures to be taken. The Commission adopts the proposal. (new Art. 107g (3))
- **Community procedure**
  - If, due to its assessment of a periodic safety update report or for other reasons, a national authority considers concrete measures necessary (such as the implementation of safety update reports, variation, suspension or revocation of an authorisation), it must inform the Commission, EMEA and other national authorities (new Art. 107i (1)).
  - The EMEA Advisory Committee is to assess whether the concerns of the national authority affect other medicinal products too. If necessary, the scope of the Community procedure is extended to such medicinal products. (new Art. 107i (2))
  - Thereupon, the EMEA Advisory Committee is to assess the matter submitted and make a recommendation for actions required (new Art. 107k).
    - In the case of medicinal products authorised in one or in more than one Member States, the coordination group will provide an opinion on the recommendations of the EMEA Advisory Committee. It then adopts by consensus the concrete measures to be taken and determines a timetable for implementation. If an opinion by consensus cannot be adopted, it is to be adopted by the Commission. (new Art. 107l (1) and (2))
    - Where medicinal products with EU authorisation are concerned, the EMEA Committee for Medicinal Products for Human Use is to adopt an opinion on the recommendation of the EMEA Advisory Committee. It also recommends the measures required. The Commission adopts the recommendation. (new Art. 107l (3) and (4))

Changes Compared to the Status Quo

- Until now, adverse reactions have been considered noxious and unintended effects derived from the authorised use of medicinal products. In future, they will also include effects derived from unauthorised use.
- The mandatory conjunction of a medicinal product authorisation with the obligation to operate a risk management system has not previously been required by EU law.
- To date, authorisation variations of medicinal products authorised in only one Member State could be adopted by national authorities. In future, the coordination group or the Commission will adopt them.
- To date, each application for the authorisation of a medicinal product had to include a detailed description of the respective pharmacovigilance system. In future, a summary will suffice, while the comprehensive pharmacovigilance system master file only has to be recorded and stored at the premises of the applicant.

Statement on Subsidiarity

According to the Commission, actions at Community level are required, since different national measures would impede the unhampered common use of safety studies and entail a splitting of the medicinal product market impeding free trade.

Political Context

The proposed Directive is part of the "pharmaceutical package" submitted by the Commission on 10 December 2008. Its content is closely related to the Regulation Proposal COM(2008) 664, which aims to strengthen EMEA's role in monitoring medicinal products in the Community.
In addition, the "pharmaceutical package" comprises a Directive Proposal on the improved protection from falsified medicinal products [COM(2008) 668; cp. CEP Policy Brief], a Communication on a renewed vision of the pharmaceutical sector [COM(2008) 666] and a Directive Proposal regarding information to the general public on medicinal products subject to medical prescription [COM(2008) 663; cp. CEP Policy Brief].

Legislative Procedure

10.12.08	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 Enterprise and Industry
Committees of the European Parliament:	Environment, Public Health and Food Safety (in charge), rapporteur: Linda McAvan (PSE Group, UK); Industry, Research and Energy; Internal Market
Committees of the German Bundestag:	Health (in charge)
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

Legislative competence:	Art. 95 TEC (Internal Market)
Form of legislative competence:	Concurrent legislative competence
Legislative procedure:	Art. 251 TEC (Co-Decision)

ASSESSMENT

Economic Impact Assessment

Ordoliberal Assessment

Pharmacovigilance finds itself caught up in the competing interests of pharmaceutical manufacturers on the one side, who wish to have new medicinal products authorised as fast as possible, and the experts on the other side, who do not want to grant authorisation until all possible risks of the medicinal product have been clearly identified. With its proposed Directive, the Commission is following a compromise: On the one hand, it adheres to most of the existing authorisation procedure; on the other hand, it intensifies the monitoring of medicinal products following their authorisation. This is in line with the estimation of the International Society of Drug Bulletins (ISDB), according to which, systematic pharmacovigilance could prevent a quarter of all undesired medical reactions and a half to one third of all drug induced deaths ("Berlin Declaration" of ISDB, 2005, p. 7).
The requirements for authorisation are mainly complemented by **the obligation to establish a risk management system for each new medicinal product**. Moreover, post-authorisation monitoring is to be reinforced. In particular, **post-authorisation requirements** and **safety studies monitored by competent authorities** are to be imposed. These measures are an important contribution to the improvement of medicinal product safety and **make it possible to react immediately to new risks**.

Impact on Growth and Individual Freedom of Choice

For the efficient monitoring of authorised medicinal products it is vital that all adverse reactions be recorded. Up till now, only a fraction of the actual adverse reactions is being reported. Therefore, the new option for patients to report suspected adverse reactions electronically is to be welcomed. However, it is somewhat doubtful, whether this will help to actually increase the number of reports, since the Proposal is limited to electronic reports, whereas 80% of the reports on adverse reactions which the Drug Commission of the German Medical Association (*Bundesärztekammer*) receives are sent by mail or fax.

Moreover, one should also not be too optimistic about the quality of the data to be collected. There are both advantages and disadvantages to the proposed simplified patient reporting. On the one hand, adverse reactions to non-presciption drugs would hardly become public without reports by patients. On the other hand, the quality of the reports, which is more or less possible to influence, are most likely to vary greatly in terms of quality.

Pharmacovigilance aims to identify adverse reactions and their future prevention. Reports which do not contribute to the identification of adverse reactions should therefore be excluded. To this end, **integrating noxious effects derived from unauthorised use into the definition is to be rejected**.

Also **the obligation imposed on manufacturers to include "essential information" in the package leaflet of medicinal products is somewhat two-edged**. It might induce patients not to read the remaining information, in particular on the dosage. This might lead to avoidable dosage errors which, in turn, might lead to unnecessary reports to pharmacovigilance systems.

The new option to fix an EU reference date for the periodic safety update reports for all medicinal products with the same active substance means that only one single assessment and expert opinion are accomplished, and to that effect is to be welcomed. The Commission expects savings to the amount of € 145 million per year.

Impact on Growth and Employment

Insignificant.

Impact on Europe as a Business Location

As the requirements for the authorisation of medicinal products have not been significantly tightened, it is not expected that Europe falls behind in the global competition for pharmaceutical research locations.

Legal Assessment

Legislative Competence

Although the proposed measures contribute significantly to serving health protection, they should also not least aim to ensure the free movement of goods in the Community. Therefore, legal competence is laid down in Art. 95 TEC (cp. ECJ, Case C-380/03, Germany ./. Parliament and Council – Tobacco Advertising, No. 40).

Subsidiarity

The EU should not decide about medicinal products authorised in only one Member State since this lacks any cross-border relevance. This must be reconsidered in the Community procedure.

Proportionality

Medicinal products bear considerable risks which can be threatening to health and life. Therefore, the obligation to establish and maintain risk management systems is a proportionate restriction of the entrepreneurial freedom of manufacturers.

Compatibility with EU Law

Unproblematic.

Compatibility with German Law

To date the German Medicines Act (AMG) does not provide for any authorisation requirements for the operation of risk management systems (§ 22 (2) No. 5 AMG) and cannot be imposed ex post. To implement the "Community procedure" requested by the Directive, the tenth clause of the AMG would have to be modified as well as the "graduated scheme" regarding pharmacovigilance based on § 63 AMG.

Alternative Policy Options

Not foreseeable.

Possible Future EU Action

Not foreseeable.

Conclusion

The proposed amendments, in particular the risk management schemes for new medicinal products and the extended powers to impose post-authorisation requirements, enable the early detection of adverse reactions and thus improve medicinal product safety. Naturally the recording of adverse reactions resulting from improper use and the placing first of "essential information" in package leaflets is problematic. The submission of purely national matters to Community procedure infringes the principle of subsidiarity.