



The new EU pharmacovigilance legislation:

Directive 2010/84/EU

and

Regulation No. 1235/2010

Guidance for Patient Organisations

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1. This document's purpose and structure

This document aims at providing information and guidance for patient organisations on the EU pharmacovigilance legislation, published in the EU Official Journal at the end of 2010. The guidance focuses on aspects of the legislation that have particular implications for patients, and will be updated following developments in the implementation process.

EPF worked closely with the EU Institutions in the process of drafting the new legislation to ensure it was patient-centred. The rules contain specific provisions to empower patients, for example through better access to information, and the opportunity to report suspected adverse reactions directly to national authorities; so it is vital that patient organisations at national level are aware of the new rules. Patient organisations can also contribute to the implementation process at national level by engaging with the responsible authorities and bodies to ensure that the provisions of the legislation are implemented in a way that is as patient-centred as possible. They also play a key role in informing their grassroots patient communities about the new rules and other issues around medicines safety, such as the importance of reporting suspected adverse drug reactions. Finally, EPF member organisations are a vital source of knowledge that will feed through EPF into the monitoring process at EU level during the next years.

This document first gives a basic overview of pharmacovigilance and its importance for patients. It then presents an overview of the new pharmacovigilance legislation, including the key provisions for patient involvement, information to patients, and measures aimed at improving the safety and quality of medicines in the EU. Finally, this document suggests opportunities for patient involvement at national and EU levels.

2. Introduction to pharmacovigilance: why is it important for patients?

The World Health Organization defines pharmacovigilance as “the science and activities relating to the detection, assessment, understanding and prevention of adverse drug effects or any other drug related problem.” (WHO, 2002) Pharmacovigilance is the system used to monitor the safety of medicines after they have been authorised¹ for use, and it plays an important role in public health and protection of patients' safety.

Pharmacovigilance monitors the way the medicines work, and their risk-benefit balance. While medicines are tested in clinical trials before marketing authorisation is granted, trials are necessarily limited in time and the number and type of patients involved. Trials are an 'artificial' environment: patients are selected according to certain criteria to avoid bias (e.g. age limitations, no other drugs, no other diseases present). This means they are not representative of real-life use. Once on the market, medicines are used by a far greater number of people, in different circumstances. Furthermore, some side effects can emerge only after a prolonged period of use.

For this reason it is crucial to continue monitoring and collect as much information as possible on how medicines work in real-life settings. Adverse reaction reporting is a

¹ See Glossary for explanation of EU marketing authorisation procedures.

fundamental part of a pharmacovigilance system: it brings further knowledge that is crucial for the safe use of a medicine, and if new risks are discovered a range of actions can be taken by competent authorities to ensure patient safety. These can range from updating the information accompanying the medicine, to suspending the marketing authorisation in case where a medicine is deemed to pose serious risks.

Adverse drug reactions are estimated as the fifth largest cause of deaths in hospital² – yet only around 10% to 25% of all adverse reactions are reported. Both patients and healthcare professionals are currently underreporting. For this reason, having clear EU-wide rules on pharmacovigilance and ensuring effective cooperation between Member States for all medicines sold in more than one Member State is fundamental to improve the safety and quality of care. The new EU rules also improve the collection of information on adverse reactions and bring new ways to encourage reporting, including more options for patients.

The competence of the EU to legislate in this area

What the EU is allowed to do and how is defined in the EU Treaties and the EU's competence in a given field. In the field of health, the EU has limited competence, defined in *Article 168* of the Treaty on the Functioning of the European Union³ (“the public health article”).

Responsibility for organisation of health systems and delivery of healthcare lies with the Member States. EU action aims to complement national policies and promote cooperation, and it must respect the principles of *subsidiarity and proportionality*.⁴ Simply put, this means that EU action is only justified if action at Member State level would not be effective enough to reach the agreed objective, and that the Union must not do more than is necessary to reach that objective.

In health, the EU generally only adopts non-binding legislative instruments such as recommendations and communications, but there are some specific areas where the EU can adopt binding legislation to harmonise national laws. One of these is to set high standards of quality and safety for medicines and medical devices. This is set out in Article 168(4)(c) and is the legal base for EU action on medicines safety, together with the Internal Market article (Article 114). The new EU legislation was put forward by the European Commission in 2008 as part of the “pharmaceutical package” – the other parts of the “package” concerned falsified medicines and information to the public on prescription medicines.⁵

The role of Member States

Member States have a central role in pharmacovigilance. They must have in place a system of pharmacovigilance to record information on suspected adverse drug reactions for all medicinal products – even in cases where the product has been misused, or used in

² Source: European Commission, http://ec.europa.eu/health/files/pharmacovigilance/ga_pharmacovigilance_2011_en.pdf

³ The consolidated version of the Treaty is available at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2010:083:0047:0200:en:PDF>

⁴ See Glossary for precise definitions of these terms.

⁵ For more information on the pharmaceutical package, see http://ec.europa.eu/health/human-use/package_en.htm

overdose. There are national competent authorities (NCA) in place to do this. Their task is to evaluate all information scientifically, consider the options for risk minimisation and prevention and, if necessary, take action regarding the marketing authorisation. They can, for example revoke it, or not renew it. NCAs can also ask for more information from the company that holds the authorisation (“the marketing authorisation holder”) to show that a positive risk-benefit balance is maintained at any time. The new legislation reinforces the pharmacovigilance requirements on Member States and strengthens their mutual collaboration.

The role of patients and health professionals

The patients’ role in actively reporting adverse drug reactions is key to building a better system of pharmacovigilance. Patients are best placed to assess the impact of a medicine on their bodies and their quality of life. High quality of information to patients is crucial, as good information on medicines and adverse drug reactions can empower patients to participate more actively in healthcare-related decisions, together with health professionals. A good patient-health professional relationship, based on trust and mutual respect, is also crucial to ensure that patients are comfortable discussing the effects of medicines with their doctor, or other health professional.

Systems for direct reporting of suspected adverse reactions by patients (or consumers) already operate in some EU Member States, notably the UK, Denmark and Netherlands, where their impact has been positive.⁶ Studies have shown that patient reports are as valuable as reports by healthcare professionals – in fact they have special added value, because patients are able to specify the circumstances in which the reaction occurred, and they often give much more detailed and nuanced descriptions. Patients also report somewhat different types of reactions than health professionals, often earlier, and they perceive the impact and severity of reactions differently.⁷

The new EU rules will allow direct patient reporting in all EU Member States. EPF strongly welcomes this: giving patients this possibility will be empowering, and it will lead to more crucial safety information being collected, and therefore to better medication safety.

A patient-centred implementation of the new EU rules that fully benefits from the added-value of patient reporting and patients’ expertise, will depend upon effective dissemination of information to patient communities about what pharmacovigilance is; how the new rules will improve medicines safety; why it is important that patients report suspected adverse reactions; and what avenues are available to do it.

⁶ See for example documents from the second pharmacovigilance stakeholder forum, European Medicines Agency, available [here](#); and the “Monitoring Medicines” project (FP7) on www.monitoringmedicines.org

⁷ See for example a report from a joint EPF-PGEU seminar, “Adverse drug reactions: moving forward together on patient safety”, 15 September 2010, available at www.eu-patient.eu/Events.

3. Key dates

- The rules within the Regulation will apply from 2 July 2012, and the provisions of the Directive will apply from 12 July 2012.
- Member States must transpose the provisions of the Directive into their national laws by October 2013.
- The Commission must report to the Parliament and Council on the shortcomings of package leaflet and summary of products by January 2013.
- The Member States have to do an audit of their pharmacovigilance system and provide a report to the Commission by September 2013 at the latest.
- The Commission will publish a report on the performance of pharmacovigilance tasks by the Member States by 21 July 2015, and thereafter every 3 years.

4. Key provisions for patients in the new EU legislation

The new EU legislation on pharmacovigilance comprises a Directive ([Directive 2010/84/EU](#)) and a Regulation ([Regulation No. 1235/2010](#)). These legal texts amend the existing EU legislative framework, which consists of Directive [2001/83/EC](#) and Regulation [726/2004](#). The existing laws are amended only as regards pharmacovigilance. The new rules were adopted by the Council of the European Union on 29 November 2010 without debate, having reached agreement with the European Parliament on first reading. The legislation was published in the EU Official Journal on 31 December 2010.

This guidance focuses on the Directive, since that is where Member States have room for manoeuvre in transposing it into their national legislations. While an EU Regulation is directly applicable and binding to every Member State (i.e. it becomes national law), Directives are binding in terms of the objectives that Member States must achieve, but it is up to the Member States to choose the measures to achieve those objectives. Directives, therefore, require a formal legislative act to *transpose* them into national law.

The pharmacovigilance legislation is an important step forward not only for medicines safety but also for patient involvement, which is embedded in the legislative text. It offers many opportunities for patient organisation involvement both at EU and national levels, including through direct reporting by patients, increased transparency, key consultations such as on the package leaflets and summary of products characteristics, a role for patients in the new Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency, and possibilities for cooperation at national level between Member State authorities and patient organisations to encourage the reporting of adverse reactions.

This section gives an overview of the most important provisions in the legislation for patients.

Direct patient reporting in all EU Member States

Patients are in the best position to know what effect a medicine has on their body, their mind, and the quality of their daily life. Health professionals are known to under-report suspected adverse events in general – and particularly in situations where drugs are being prescribed off-label, or in case of medication errors. Patients, moreover, do not always feel comfortable talking to their doctor or pharmacist about adverse reactions – the reaction may be intimate, such as a sexual or psychological problem, or the doctor may appear uninterested in the patient’s concerns.

Direct patient reporting (DPR) refers to the possibility for patients to report directly suspected adverse drug reactions to competent authorities. DPR is already in place in several EU countries, but the systems are rather different and some of them are more developed than others. The new EU law will bring this opportunity to patients in all Member States.

DPR is a tool to encourage “spontaneous reporting” by patients and consumers of suspected adverse drug reactions. “Spontaneous” means that a patient themselves takes the initiative to report a reaction. Spontaneous reporting is recognised as a key tool for better medicines safety; it is also in itself an expression of patient empowerment as well as a means of developing health literacy and becoming empowered.

Feedback from the established systems is consistently that patient reporting is equal quality to professional reporting⁸ and that it actually adds value because it is based on the direct experience of the users and provides richer detail.⁹ Studies show that patient reporting can lead to earlier detection of adverse reactions, and the discovery of new reactions, as patients often report different reactions than professionals do.

In addition to reporting adverse reactions through their healthcare professionals (e.g. doctors or pharmacists), once the law is implemented patients will have the option to report directly to the national competent authorities if they prefer. This will be done through web-portals that Member States will be required to set up, and through at least one other reporting means of the Member State's choice. Patients’ reports will go to their national medicines regulators, who will forward them to Eudravigilance.

Member States must take appropriate measures to facilitate patient reporting of adverse reactions to their national competent authority. They may involve patient organisations for this purpose. They will have to involve individual patients in the follow-up of reports in order to obtain accurate data, and they will have to take all necessary measures to identify products suspected of provoking adverse reactions.

More effective collecting of medicines safety information

Member States are responsible for recording suspected adverse reactions on their territories, whether reported by patients or healthcare professionals. They must audit their

⁸ See “*The importance of direct patient reporting of suspected adverse drug reactions: a patient perspective*” Claire Anderson, Janet Krska,² Elizabeth Murphy³ & Anthony Avery, *British Journal of Clinical Pharmacology*, Volume 72, Issue 5, pp 806-822, November 2011.

⁹ See example from

http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2010/08/WC500095890.pdf

systems to make sure they have in place the necessary expertise. They must report the results to the Commission by 21 September 2013, and thereafter every 2 years.

Member States will in future collect information on all adverse reactions, even in cases where the product is not used within the terms of its marketing authorisation – that is, also for cases of overdose, misdose, abuse and medication errors. Member States are also invited to consider the *environmental impact* of medicines.

At EU level, the existing [Eudravigilance database](#) will be developed to become the single point of receipt for all pharmacovigilance information in the EU, including adverse drug reaction reports. All reports from Member States and from companies must be submitted to Eudravigilance, within 15 days if considered as serious, or within 90 days if considered as non-serious.¹⁰ Eudravigilance will notify all Member States electronically. The European Medicines Agency will prepare an annual report on the functioning of the database for the European Parliament and the Council.

Companies will still need to set up a pharmacovigilance system for monitoring and supervision of their authorised products, when applying for marketing authorisation. The requirements of applications are simplified so that only key elements of the system must be submitted rather than a detailed description. However, companies must maintain a detailed file available for possible inspections by competent authorities.

Furthermore, companies *may not refuse reports of suspected adverse reactions* from health professionals or patients, provided in an appropriate format. Companies may also be required, as part of the conditions for marketing authorisation, to conduct post-authorisation safety and efficacy studies, and to operate a risk management system.

Improvements to the medicines package leaflet and labelling

General improvements will be made to medicines packaging and the patient information leaflet, which will also support patient reporting.

For all medicinal products, a *standardised text* will be included in the package asking patients to communicate any suspected adverse reactions to their doctor, pharmacist, other healthcare professional, or directly to the national authorities. The different options for reporting will be explained and relevant contact details given.

Products under additional monitoring (such as products with new active substances, biological medicines, and other products if deemed necessary for the marketing authorisation) will be identified by a black symbol and explanatory sentence on the packaging.

The European Medicines Agency is already doing ongoing work with patients and consumers to improve the patient leaflet templates, and EPF is involved in this working group. Notwithstanding the above improvements, two years after the publication of the legislation, the Commission will present a *review on the shortcomings of the patient information leaflet* and summary of product characteristics, which are widely considered not to be user friendly.

¹⁰ See Glossary for usage of the term “serious” adverse event.

The Commission will consult stakeholders and present proposals on how these documents could be improved in order to better meet the needs of patients and health professionals.

Better information on pharmacovigilance to the public

The new legislation offers greater transparency of the pharmacovigilance system, and better access to information through different means. The aim is a system that enjoys the confidence and trust of patients and the general public. Several inter-linked information resources will be set up:

Member States will be obliged to set up and maintain ***national medicines web-portals***. The following information has to be made available through these portals (at a minimum):

- Publicly available versions of the assessment reports with their summaries
- Summaries of product characteristics
- Package leaflets
- Summaries of the risk management plans for authorised medicinal products
- The list of medicinal products that are subject to additional monitoring
- Information on the different ways of reporting suspected adverse reactions to the national competent authorities by healthcare professionals and patients

The national web-portals will be linked to a ***European medicines portal***, to be developed by the EMA, which will provide further information. This will include:

- information about the EMA Pharmacovigilance Risk Assessment Committee and its meetings;
- post-authorisation studies;
- summaries of risk management plans;
- list of locations of the pharmacovigilance master files;
- information about Union reference dates and frequency of submission of periodic safety update reports;
- protocols and public abstracts of results of the post-authorisation safety studies;
- information on the initiation of urgent union procedures (including the active substances or medicinal products concerned, the issue being addressed, any public hearings and information on how to submit information and participate in public hearings;
- the conclusions of assessments, recommendations, opinions, approvals and decisions taken by the PRAC and CHMP and by the Coordination Group, the national competent authorities and the Commission in the framework of assessment of periodic safety update reports.

The ***Eudravigilance database*** will be partially accessible to the public, health professionals and research organisations. The website for public access to medicines safety data will be available at www.adrreports.eu.

EPF has been actively contributing to an EMA working group to advise on the implementation of the [Eudravigilance access policy](#) to ensure the clarity and user-

friendliness of information. EPF is also contributing to the development of a standardised web-form for the reporting of suspected reactions.

The new legislation also allows for **public hearings** on medicines to be held at the EMA in cases of specific, serious safety concerns. The hearings are a tool to give a voice to stakeholders in the scientific deliberation process, to respond to demands for more transparency of the scientific review process, and to build trust in the Agency by opening up its procedures to the public. Public hearings will give access to public testimony or comment regarding therapeutic effects and clinical practice of medicines under investigation. They will be announced on the European medicines web-portal.

Clearer responsibilities and better coordination between Member States

i. Strengthened role for the European Medicines Agency

the role of the European Medicines Agency in improving coordination between Member States is strengthened. The new rules reinforce the existing *Co-ordination Group for Mutual Recognition and Decentralised Procedures*, composed of national experts, that is responsible for agreeing and monitoring risk management systems. The mandate of the group is enlarged and it will in future examine questions related to pharmacovigilance of all medicines authorised by Member States, in addition to examining questions relating to the marketing authorisation of products authorised in two or more Member States.

A new *Pharmacovigilance Risk Assessment Committee (PRAC)* will be set up at the EMA to replace the current Pharmacovigilance Working Party. The PRAC will be composed of Member State experts and of experts nominated by the European Commission (including one representative and one alternate for patients and health professionals). The PRAC will advise the Coordination Group and the Committee for Medicinal Products for Human Use (CHMP) on all aspects of the assessment of pharmacovigilance data after the authorisation of a medicine. (The CHMP will remain responsible for issuing an opinion on the product.) The PRAC will cover all aspects of risk management, including detection, minimisation of risks of adverse reactions, design and evaluation of post-authorisation studies, and recommendations on *urgent procedures*. For more information please see [this presentation](#) by the EMA.

The legislation also provides for *better coordination of communications on risk*. Safety announcements related to a medicine authorised in more than one Member State will be coordinated by the EMA. In addition, decisions on whether to trigger an *urgent procedure* to withdraw a medicine or suspend its authorisation will now have to be reached within a defined timeframe: 90 to 105 days to reach a decision.

ii. Clearer responsibilities for companies and national authorities

The company which holds the marketing authorisation for a medicine (“marketing authorisation holder”) may be required to conduct *post-authorisation safety and efficacy studies* once a medicine is on the market. They must inform the national authorities or the EMA if a new risk appears, or if there is any change to the risk-benefit balance of a product.

The new legislation clarifies and strengthens the responsibility of marketing authorisation holders: they must have in place permanently a person who is qualified and responsible for pharmacovigilance, and they must maintain a pharmacovigilance master file. They must also record all spontaneous reports of adverse drug reactions submitted by patients and healthcare professionals, and submit this information to the Eudravigilance database within 15 days for serious¹¹ suspected reactions or 90 days non-serious ones.

Supervision of post-authorisation studies by *national competent authorities* is strengthened and clearly defined by law, rather than guidance as was the case before. The new rules give them the power to impose on the marketing authorisation holder the obligation to conduct post-authorisation studies; in particular, they may require safety and efficacy studies at the time of authorisation or later if an important safety concern emerges.

5. Impact on patient organisations at national and EU level

At European level, EPF will engage with the Commission and where necessary invite the input of its membership, in monitoring the implementation of the new legislation. At national level, the legislation does not directly oblige Member States to involve patient organisations, but it does encourage this.

At the EU level, EPF will continue to work in close collaboration with the Commission and EMA as well as various other stakeholder groups such as those representing doctors and pharmacists. EPF believes that patient organisation action at national and EPF levels will be highly complementary; EPF invites its members to engage with their national authorities and to inform EPF of developments in your country. EPF will seek its members' views on specific developments, but would also encourage you to get in touch at any time if you have relevant information, feedback or queries.

The following tables summarise the areas where patient organisations can provide input at both levels, and ensure that information flows to grass-roots patient communities in different Member States and disease-areas.

¹¹ See Glossary for usage of the term “serious”.

Summary table – opportunities for patients’ information and involvement at national level

Area to monitor/give input	Relevance for patient organisations
<i>Encouraging reports by adverse drug reactions</i>	<ul style="list-style-type: none"> ○ The Directive states Member States “may” involve patient organisations to encourage reporting by patients. Patient organisations can ask to be involved in this as a partner, provide advice and support for an information campaign. For example, to increase the motivation of patients to report suspected reactions, some kind of feedback should be given to individual patients who do report about how the information is used and about the value of the report. ○ In addition to structured web-forms, Member States have to provide at least one other way for patients to report directly to the national competent authorities. Patient organisations can suggest appropriate ways to ensure that all patients can report, not only those with access to Internet. ○ Patient organisations can offer help in preparing guidelines for implementation of direct patient reporting, including ways to report that are offered in your Member State, what sort of information should be captured in the reporting system, what information is needed by the public, etc.
<i>Transparency on pharmacovigilance, public awareness</i>	<ul style="list-style-type: none"> ○ Patient organisations can give advice concerning the set-up of national medicines web-portals to ensure the information is clear, meets patients’ needs and is user-friendly. Patient organisations can suggest other information that would be useful to include although not strictly required by the rules. ○ In addition to public information campaigns, patient organisations play a key role supporting long-term patient awareness about pharmacovigilance, as they are in regular and close contact with grass-roots patient communities. Make sure the national authorities are aware of your activities and their added value.
<i>Urgent union procedure</i>	<ul style="list-style-type: none"> ○ Patient organisations can give their views on temporary or long-term measures to ensure patients’ safety when a Member State initiates an urgent union procedure about a specific drug.
<i>Regular audit of the Member State pharmacovigilance system (compulsory, first audit by September 2013)</i>	<ul style="list-style-type: none"> ○ Patient organisations can give their perspective to the national authorities about what works in the pharmacovigilance system and what needs improvements from a patient’s perspective.

Summary table – opportunities for patients’ information and involvement at European level

Area	Opportunities for input through the European Patients’ Forum
<i>Clear, high-quality information to patients</i>	<ul style="list-style-type: none"> ○ Consultation by the European Medicines Agency on the web-portal for the dissemination of information on medicinal products authorised in the Union (the EU medicines portal) ○ Consultation by the European Commission on the patient information leaflet and summary of product characteristics, and suggestions to improve their user-friendliness. The Commission must report to the Parliament and Council on the shortcomings of package leaflet and summary of products by January 2013.
<i>Encouraging direct patient reporting and awareness of pharmacovigilance</i>	<ul style="list-style-type: none"> ○ EPF has called for information/awareness resources to be developed by the European Commission/European Medicines Agency. ○ EPF has called for specific training programmes on pharmacovigilance for patient groups, to equip them to contribute more effectively into the implementation and to work in partnership with national authorities more generally. ○ EPF will involve the membership in any future developments.

6. Glossary of terms

(Suspected) Adverse drug reaction (ADR): Any unexpected or dangerous reaction to a medicine. An unwanted effect caused by the administration of a medicine. The onset of the adverse reaction may be sudden or develop over time.

Serious vs. non-serious adverse reaction: Events are categorised as ‘serious’ or ‘non-serious’ for reporting purposes. A serious event poses a threat to a patient's life or functioning. This is not synonymous with “severe” – a term often used to describe the intensity of a specific event for the patient (as in mild, moderate, or severe). Thus a headache as an adverse reaction may be severe, but not a serious reaction for reporting purposes.

The EMA defines a serious adverse event as any untoward medical occurrence that at any dose results in death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect.¹²

Black symbol: Products containing new active substances will be identified for 5 years by a black symbol on the medicine packaging/patient information leaflet. If the product is subject to *additional monitoring* this period can be extended. Additional monitoring means that the reports database is checked more often to detect any *signals* as early as possible. The black symbol and its accompanying explanatory text will be developed by the European Medicines Agency.

EudraVigilance: Eudravigilance is an electronic database maintained by the European Medicines Agency. It was established in 2001, and currently contains adverse reactions reports on authorised and licensed medicines from across Europe. This information is shared by national competent authorities. It also contains reports from serious adverse reactions from clinical trials. From July 2012 onwards, the role of Eudravigilance will be expanded: It will become the single point of receipt for all pharmacovigilance information for medicines for human use authorised in the EU. Companies and Member States will report reactions directly to Eudravigilance, which will immediately notify all Member States electronically. The database will be accessible to Member States and the European Commission, and will also be partially opened to healthcare professionals and the public (patients). The Eudravigilance website is at: www.eudravigilance.eu See also: www.adrreports.eu

European Medicines Agency (EMA): A decentralised body of the European Union, its main responsibility is to protect and promote public health. Its role is to evaluate and supervise medicines.¹³

- **Committee for Medicinal Products for Human Use (CHMP):** This committee prepares the Agency's opinion on all questions related to medicines for human use. It is

¹²

http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf

¹³ European Medicines Agency website, *what we do*:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000091.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028a42

composed of experts nominated by the 27 Member States, Norway and Iceland in consultation with the Agency (1 member, 1 alternate for each country), and 5 co-opted members chosen for their specific expertise.¹⁴

- *Pharmacovigilance Risk Assessment Committee (PRAC)*: A committee established by the 2010 Pharmacovigilance legislation, it is composed of experts for the EU Member States, and other experts, including representatives of patients and health professionals. The PRAC will advise the Coordination Group and the CHMP on all aspects of the assessment of pharmacovigilance data after the authorisation of a medicine. The mandate of the PRAC will cover all aspects of risk management of the use of medicinal products for human use, including detection, assessment, minimisation and communication relating to risk of adverse reactions. The PRAC will give recommendations as part of any EU-wide post-authorisation assessment based on pharmacovigilance data, and recommendations on risk management systems and monitoring their effectiveness.¹⁵
- *Coordination Group*: The Coordination Group for Mutual Recognition and Decentralised Procedures (human), also known as CMDh, was set up in 2004 to examine any question related to marketing authorisation in two or more Member States, in accordance with the decentralised and mutual recognition procedures for authorisation. Its role is to consider cases of disagreement between Member States involved in a mutual recognition or decentralised procedure on the assessment report, the summary of product characteristics, the labelling or the package leaflet on the grounds of “potential serious risk to public health”. The CMDh also establishes a yearly list of medicinal products for which a harmonised summary of product characteristics should be drawn up, to promote harmonisation of marketing authorisations across the Community. The CMDh is composed of one representative per Member State, including Norway, Iceland and Liechtenstein.¹⁶

European Public Assessment Report (EPAR): This is a full scientific assessment report which is published by the European Medicines Agency for each medicine which is granted a centralised marketing authorisation in the European Union. A public summary of the EPAR is available for each of these medicines on the EMA website.

Good Pharmacovigilance Practice: A set of guidelines on each step in the pharmacovigilance process which applies to marketing authorisation holders, the European Medicines Agency and national competent authorities.¹⁷

¹⁴ European Medicines Agency, Committee for Medicinal Product for Human Use:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000094.jsp

¹⁵ The Pharmacovigilance Risk Assessment Committee, Roberto de Lisa, European Medicines Agency:

http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/06/WC500108031.pdf

¹⁶ Co-ordination group for mutual recognition and decentralised procedures website:

<http://www.hma.eu/cmdh.html>

¹⁷ European Medicines Agency, Good Pharmacovigilance practices (where all guidelines are available)

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_00034_5.jsp&mid=WC0b01ac05804fcd1&jsenabled=true

Marketing authorisation: To place a medicine on the market in the EU, a company must obtain a marketing authorisation. Once the application is submitted, the competent authority examines the risk-benefit balance of the medicine, assessing its safety, quality and efficacy.

There are several routes to apply for EU marketing authorisation:

- *The centralised procedure*, where one application is made to the European Medicines Agency (EMA). The EMA's scientific committee evaluates the product and adopts an opinion on whether the medicine should be marketed or not. The opinion is transmitted to the European Commission, which has the authority for granting the marketing authorisation. The central marketing authorisation is valid throughout the EU as well as in Iceland, Liechtenstein and Norway.

The centralised procedure is compulsory for medicines for treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases; biotechnology medicines; advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines; officially designated orphan medicines.

- *The national authorisation procedure*, where the authorisation is obtained from the national competent authority of one Member State and is valid only in that Member State. Each EU Member State has its own procedures for authorisation of medicines within their own territory.
- *The decentralised procedure*, where companies can apply for simultaneous authorisation in more than one EU country of a medicine that has not yet been authorised in any EU country (and that do not fall within the mandatory scope of the centralised procedure).
- *The mutual recognition procedure*, where companies that already have a medicine authorised in one EU Member State can apply for this authorisation to be recognised in other EU countries. This is dealt with by the Co-ordination Group for Mutual Recognition and Decentralised Procedures.¹⁸

The decentralised/mutual recognition procedures apply to most conventional medicinal products.

National Competent Authorities (NCAs): They are national agencies that are responsible for the evaluation and monitoring of medicines at national level.¹⁹

Pharmacovigilance Master File: Marketing authorisation holders (companies, either manufacturers or importers of medicines) will have to keep and maintain a master file containing a detailed description of the pharmacovigilance system they use for one or more medicinal product, in a declared location. It has to be made available to competent

¹⁸ Source: European Medicines Agency. More information available at

http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp&mid=WC0b01ac0580028a47

¹⁹ The full list is available on the European Medicines Agency website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000155.jsp&mid=WC0b01ac0580036d63

authorities upon request. Required contents and maintenance of the master files will be further detailed through implementing measures.²⁰

Periodic Safety Update Reports (PSURs): These reports aim at giving updates on the safety of a product, from the experience acquired worldwide. They must contain a summary of data relevant to the risk-benefit balance of a medicine, a scientific evaluation, and data related to volume of sales, prescription and exposure of the population. For products placed on the market they have to be submitted every six month during 2 years, once a year for 2 years thereafter, and every 3 years after this. The agency and the European Commission will maintain a repository of these reports and can make it available to national authorities.

Urgent union procedure: This is an alert procedure which has to be triggered by either the Commission or a Member State, if there are serious concerns related to the medicine, including a new contraindication or change in the dosage recommendation. The EMA will publicly announce the procedure, and give information on the product concerned, upon receipt of scientific information. The European Commission can ask Member States to take temporary urgent measures.

Risk management plan: According to the European Medicines Agency, an EU risk management plan:

- *“Describes what is known and not known about the safety profile of a medicine;*
- *Plans how to characterise further the safety profile of the medicine;*
- *Puts in place measures to prevent or minimise risks associated with the product and assesses the effectiveness of those interventions;*
- *Documents the need for efficacy studies and maximises the benefit-risk balance of the product for the individual patient and for the target population as a whole and to facilitate integration of benefit-risk planning.”²¹*

Signal: Reported information on a possible causal relationship between an event (either adverse or beneficial for the patient) and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.”²²

Subsidiarity and proportionality: The principle of *subsidiarity* is defined in Article 5 of the Treaty on European Union (TEU). Subsidiarity means that decisions must be taken as closely as possible to the citizen. The Union in does not take action, except in the areas that fall within its exclusive competence, unless it is demonstrably more effective than action taken at national, regional or local level. The principle of subsidiarity is closely related to the principle of *proportionality*, which requires that any action by the Union should not go beyond what is necessary to achieve the objectives of the Treaties. Following the entry into force of the Treaty of Lisbon, the principle of subsidiarity must be respected in all draft

²⁰ http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/10/WC500117083.pdf

²¹ http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2011/04/WC500105323.pdf

²² Edwards IR, Biriell C. Drug Safety 1994;10:93-102

legislative acts, and national parliaments can object to a proposal on the grounds that it breaches the principle.

Summary of products characteristics (SPC): This is a summary submitted with the application for marketing authorisations which sets out the details of the use of the product, including the therapeutic indication, dosage, how to administer, contraindications, precautions for use etc., and its composition. The SPC forms the basis of information for the healthcare professionals and for the patient information leaflet.²³

Transposition: An *EU Directive* sets out general rules and objectives but leaves Member States the choice as to how to attain them. Member States will therefore have to transpose the EU law into their national laws. This process is carried out by national governments and parliament and may involve local authorities. Member States will provide to the European Commission tables to show the link between the provisions in the Directive and the national dispositions. They have until October 2013 to adopt the necessary dispositions into their national law. *Regulations* do not need to be transposed as they are directly applicable law in Member States.²⁴

7. Links for further information

Directive 2001/83/EC on the Community code relating to medicinal products for human use:

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:en:PDF>

Directive 2010/84/EU amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use:

http://ec.europa.eu/health/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf

Regulation (EC) No.726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency:

<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF>

Regulation (EU) No.1235/2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products:

http://ec.europa.eu/health/files/eudralex/vol-1/reg_2010_1235/reg_2010_1235_en.pdf

Eudravigilance database: <http://eudravigilance.ema.europa.eu>

European Commission – Questions and Answers on Pharmacovigilance:

²³ http://ec.europa.eu/health/files/eudralex/vol-2/c/spcguidrev1-oct2005_en.pdf

²⁴ http://ec.europa.eu/governance/better_regulation/transp_eu_law_en.htm

http://ec.europa.eu/health/files/pharmacovigilance/qa_pharmacovigilance_2011_en.pdf

European Medicines Agency:

- EMA main web page:
<http://www.ema.europa.eu>
- EMA webpage on the pharmacovigilance legislation:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000491.jsp&mid=WC0b01ac058033e8ac&jsenabled=true
- EMA pharmacovigilance implementation plan:
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500121837.pdf

EMA stakeholder forums: The European Medicines Agency organised a number of stakeholders forums where the key features of the new legislation were presented and discussed. The agendas, presentations and reports from the forums are available on the EMA website:

- First stakeholder forum:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2011/04/event_detail_000413.jsp&mid=WC0b01ac058004d5c3
- Second stakeholder forum:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2011/06/event_detail_000423.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c3
- Third stakeholder forum:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2011/10/event_detail_000541.jsp&mid=WC0b01ac058004d5c3
- Fourth stakeholder forum:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/events/2012/02/event_detail_000554.jsp&mid=WC0b01ac058004d5c3

European Patients' Forum (EPF) and Pharmaceutical Group of the European Union (PGEU) event on patients' direct reporting, September 2010, seminar report:

<http://www.eu-patient.eu/Events/European-Parliament-Event-on-Direct-Patient-Reporting/>

European Patients' Forum (EPF) website:

www.eu-patient.eu

The European Patients' Forum (EPF) was founded in 2003 to become the collective patients' voice at EU level, manifesting the solidarity, power and unity of the EU patients' movement. EPF currently represents 54 member organisations, which are chronic disease-specific patient organisations working at European level, and national coalitions of patients organisations. Collectively they reflect the voice of over 150 million patients living with various chronic diseases in the European Union. EPF's vision for the future is high quality, patient-centred, equitable healthcare throughout the European Union.



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Disclaimer: The content of the *EPF Guidance for Patient Organisations on the new EU Pharmacovigilance legislation* reflects only the author's views and the Executive Agency is not responsible for any use that may be made of the information contained therein.