EUROPEAN PARLIAMENT

Medicinal products in the European Union

The legal framework for medicines for human use

IN-DEPTH ANALYSIS

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This paper gives a general overview of several aspects of EU legislation on human medicines. It describes relevant regulatory rules and procedures, identifies the actors involved, and highlights current practices. The document also takes stock of stakeholder views. It concludes with a snapshot of an emerging approach in medicines approval.

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EXECUTIVE SUMMARY

A high level of protection for human health is a central objective of European Union (EU) public health policy. To guarantee this objective, high standards of quality and safety for medicinal products are essential. Although pharmaceuticals are primarily regulated at the national level by the Member States, there is a large body of EU legislation in the field.

A medicine must be authorised before it can be placed on the market. In the EU regulatory system, there are several routes for obtaining marketing authorisation: either at European level (the centralised procedure) or at national level (the decentralised and mutual-recognition procedures). Under the centralised procedure, EU authorisation is granted by the European Commission via an application to the European Medicines Agency (EMA). The EMA coordinates the assessment of the quality, safety and efficacy of medicinal products. It draws up scientific opinions for the evaluation of such medicines for the EU institutions and the Member States. The EMA also coordinates Member States' activities in connection with the monitoring of medicines for safety once they have been placed on the market (pharmacovigilance), and manages the internet-based information system created to this effect. In addition, the EMA coordinates Member States' supervision and inspection of manufacturers.

Two special authorisation procedures exist outside the conventional routes: Article 58 applications (for medicines used exclusively outside the EU) and the procedure for compassionate use. There are specific regulatory rules for 'orphan medicines', as well as paediatric, geriatric, advanced-therapy, herbal, homeopathic and non-prescription medicines.

A number of instruments have been put in place to guarantee that a medicinal product fulfils the legal requirements in terms of quality, safety and efficacy. These are the principles of good manufacturing, good distribution, and good pharmacovigilance practices. They are complemented by information for patients and protection against falsified medicines. With a view to allowing early access to medicines, a new concept – the adaptive pathways approach – has recently taken shape. It is based on existing regulatory procedures such as compassionate use, and involves progressive access to medicines in advance of full authorisation. This could particularly benefit patients who have a medical condition not adequately addressed by an existing therapy.

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List of main acronyms used

ATMP	advanced-therapy medicinal product
CAT	Committee for Advanced Therapies
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
CVMP	Committee for Medicinal Products for Veterinary Use
EMA	European Medicines Agency
EPAR	European public assessment report
GDP	Good distribution practice
GMP	Good manufacturing practice
GVP	Good pharmacovigilance practice
HCV	Hepatitis C virus
HMPC	Committee on Herbal Medicinal Products
NCA	national competent authority
OTC	over-the-counter medicine
PDCO	Paediatric Committee
PRAC	Pharmacovigilance Risk Assessment Committee
WHO	World Health Organization

Definitions[1]

Active substance: the substance responsible for the activity of a medicine.

Adaptive pathways/progressive licensing/staggered approval: gradual procedure for the authorisation of a new medicine, with repeated cycles of data gathering, evaluation and regulatory approval. It allows patients earlier access to new therapies, particularly in situations with a high unmet medical need.

Autoimmune disorder: occurs when the body's immune system attacks and destroys healthy body tissue by mistake. There are more than 80 types of autoimmune disorders.

Biocidal product/biocide: a product that is intended to destroy or otherwise exert a controlling effect on any harmful organism by chemical or biological means. Examples include disinfectants and insecticides.

Claims: (medicinal) claims that a medicine can treat or prevent disease, or interfere with the normal operation of a physiological function of the human body.

Compassionate use: the use of an unauthorised medicine prior to approval in seriously ill patients under strictly controlled conditions.

Marketing authorisation: the approval to market a medicine in one, several or all EU Member States.

Marketing authorisation holder: the company or other legal entity granted authorisation to market a medicine in one, several or all EU Member States.

Neurodegenerative disease: a condition characterised by progressive nervous system dysfunction. Examples include Alzheimer's disease and other dementias, stroke, Parkinson's disease and multiple sclerosis.

Orphan medicine: a medicine for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that is rare (affecting not more than five in 10 000 people) or where the medicine is unlikely to generate sufficient profit to justify research and development costs.

Paediatric investigation plan: the plan describing how a medicine should be studied in children.

Pharmacovigilance: science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

Recombinant gene: a stretch of DNA created in the laboratory, bringing together DNA from different sources.

Sponsor: any legal or natural person 1) having obtained designation of a medicinal product as an orphan medicine; 2) taking responsibility for the initiation, management and financing of a clinical trial.

Unmet medical need: a medical condition that is not addressed adequately by an existing therapy.

[1] Based mainly on: EMA portal (glossary and webpages on adaptive pathways), EUPATI glossary, European Commission's Public health portal, MedlinePlus.

1 Introduction and issue definition

The fundamental aim of the rules for medicinal products in the EU is to safeguard public health – an aim that should be attained without hindering development of the European pharmaceutical industry or trade in medicinal products. This **twofold objective of protection of public health and free movement of medicines** is the common thread of the entire legal framework for medicinal products. EU pharmaceutical legislation covers the whole lifecycle of a medicinal product, from manufacture, to clinical trials, to marketing authorisation, to pharmacovigilance and patient information. It is a comprehensive and complex set of rules.

1.1 What are medicinal products for human use?

The legal basis for medicinal products is Article 168 of the Treaty on the Functioning of the European Union (TFEU). It stipulates that 'a **high level of human health protection** shall be ensured in the definition and implementation of all Union policies and activities'.[2] The European Parliament and the Council shall contribute to this objective by adopting 'measures setting **high standards of quality and safety for medicinal products** and devices for medical use'.

More specifically, Article 1(2) of Directive 2001/83/EC[3] establishes the following **definition** of medicinal product:

> *(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or*
>
> *(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.*

Subparagraph (a) relates to the **presentation** of the medicinal product and to the **claims** made for it. Subparagraph (b) concerns its **function and intended use**.[4] According to settled case law[5] of the European Court of Justice (ECJ), 'a product is a medicinal product if it falls within either of those two definitions'.

However, an increasing number of products may fall within the scope of two definitions – of medicinal products on the one hand, and of food products/food supplements, medical devices, biocides or cosmetics on the other. These are called **borderline products**. Article 2(2) therefore states:

> *In cases of doubt, where, taking into account all its characteristics, a product may fall within the definition of a 'medicinal product' and within the definition of a product covered by other Community legislation the provisions of this Directive shall apply.*

In other words, when there is uncertainty over the classification of a product, the stricter regime of medicinal products applies, with the ultimate aim being to protect the user. Borderline products will not be addressed in this analysis.

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2 Consolidated version of the Treaty on the Functioning of the European Union.

3 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

4 A Guide to what is a medicinal product, UK Medicines and Healthcare Products Regulatory Agency (MHRA) Guidance Note No. 8, rev. November 2012.

5 See, for instance, the recent judgment of the Court of 10 July 2014 in joined cases C-358/13 and C-181/14.

1.2 Milestones

The first Community rules on medicinal products for human use date back 50 years. Beginning with **Council Directive 65/65/EEC**,[6] which was introduced in the wake of the thalidomide disaster, the then-European Economic Community began developing structured legislation. The legal framework has since been continuously updated. The first steps towards joint EU marketing authorisation were taken in 1975[7] through a multi-state procedure and the establishment of a common Committee for Proprietary Medicinal Products. The European Agency for the Evaluation of Medicinal Products (EMEA), the predecessor of the European Medicines Agency (EMA), was founded in 1995. In 2001, **Directive 2001/83/EC** (the Community Code Directive) was adopted, one of the centrepieces of EU pharmaceutical legislation. It contains provisions for the authorisation, manufacture and distribution of medicines in the EU. **Directive 2001/20/EC**[8] (the Clinical Trials Directive), also from 2001, lays down requirements for the conduct of clinical trials in the EU. In the framework of a review of EU pharmaceutical legislation, **Regulation (EC) No 726/2004**[9] (the EMA Regulation) introduced the centralised authorisation procedure and established the EMA. Major revisions were proposed with the pharmaceutical package[10] from 2008, which came into effect with **Regulation (EU) No 1235/2010**,[11] **Directive 2010/84/EU**[12] and an Implementing Regulation (together known as the 'new pharmacovigilance legislation'), as well as with **Directive 2011/62/EU**[13] (the Falsified Medicines Directive). **Regulation**

EudraLex

The entire body of EU medicines legislation (EudraLex) is compiled in 'The Rules Governing Medicinal Products in the European Union'. The legal basis for human medicines is collected in volume 1, while the remaining volumes contain a series of scientific guidelines supporting this legislative framework. They can be consulted on the European Commission's EudraLex webpage with an integrated search engine.

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6 Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products.

7 Second Council Directive of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products.

8 Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

9 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.

10 Originally comprising three sets of proposals, one of which (on public information on medicines) was later withdrawn.

11 Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 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.

12 Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use.

13 Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.

EU No 536/2014[14] (the new Clinical Trials Regulation) was adopted in 2014, to enter into force no earlier than 28 May 2016. It will simplify procedures and enable cross-border cooperation in international clinical trials. In addition, separate legislative acts cover specific medicinal products, such as orphan medicines (2000), traditional herbal medicines (2004), paediatric medicines (2006) and advanced-therapy medicines (2007).

2 The EU regulatory system for medicinal products

Medicines can only be marketed in the EU after they have been authorised – and to be authorised, they must undergo strict testing and an assessment of their quality, safety and efficacy. The relevant provisions are primarily laid down in Directive 2001/83/EC and Regulation (EC) No 726/2004. Depending on the type of medicine, a marketing authorisation, a certificate of registration or a certificate of traditional-use registration must be obtained (see points 3.5 and 3.6 below). Granting of the authorisation or certificate is proof that the medicine complies with the required standards.

The EU regulatory system for medicines consists of:

- the medicines regulatory authorities ('national competent authorities', NCAs) in the 31 Member States of the European Economic Area (EEA);[15]
- the European Medicines Agency;
- the European Commission (DG SANTE).

The system operates as a network that pools expertise, exchanges information and shares best practice. It aims to guarantee the smooth regulation of medicines across the EU and avoid duplication of effort.[16] The heads of the national competent authorities meet four times a year with the EMA and the Commission in a voluntary (non-statutory) forum, the Heads of Medicines Agencies (HMA), to discuss issues of strategic importance for the network.

Pharmaceuticals portfolio reshuffle

On taking up office, European Commission President Jean-Claude Juncker had initially announced that he would move the responsibility for pharmaceuticals and the EMA to the Internal Market Commissioner. However, as this decision met with strong opposition both from Parliament and health stakeholders, the remit was returned to the health portfolio of Commissioner Vytenis Andriukaitis, within the Health and Food Safety DG (SANTE).

2.1 European Medicines Agency: role, tasks and functioning

The European Medicines Agency (EMA) is a decentralised EU agency located in London. It was founded in 1995 as the European Medicines Evaluation Agency (EMEA) and has been operating since 2004 on the basis of Regulation (EC) No 726/2004.

The EMA's role in the EU regulatory system for medicines is one of advice and coordination: it advises the Member States and the EU institutions on any question relating to medicinal products, and it coordinates the scientific evaluation, or

[14] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

[15] EEA: the 28 EU Member States plus Iceland, Liechtenstein and Norway. In the following, when referring to the procedures for the granting of a marketing authorisation in the EU, it is implicit that these apply equally to all EEA Member States.

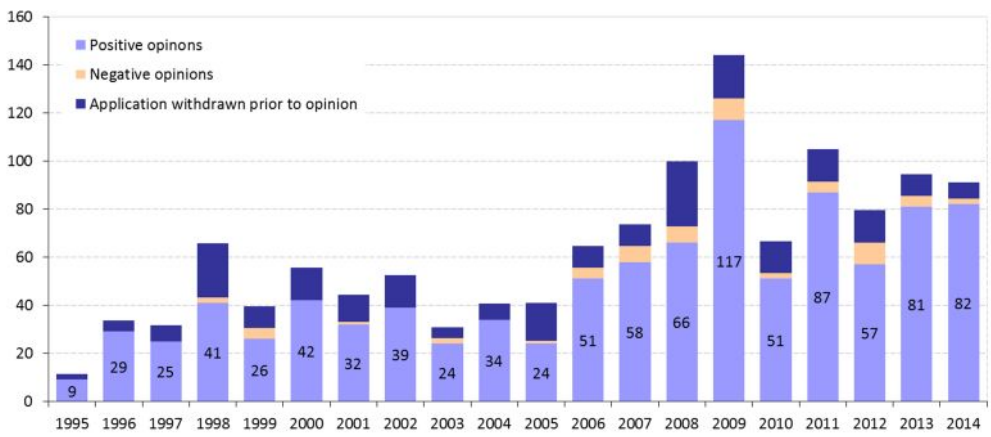
[16] EMA booklet, 'The European regulatory system for medicines and the European Medicines Agency – A consistent approach to medicines regulation across the European Union'.

assessment, of the quality, safety and efficacy of medicinal products developed by pharmaceutical companies in the EU before they are placed on the market.

The main task of the EMA is to draw up scientific opinions for the evaluation of such medicines for the EU institutions and the Member States. This task is carried out by a large pool of around 4 500 European experts[17] mostly sourced from the medicines regulatory authorities in the Member States. They take part in the EMA's assessment teams, working parties and advisory groups, or participate as members nominated by the national competent authorities in the seven scientific committees:

- Committee for Medicinal Products for Human Use (CHMP)
- Committee for Medicinal Products for Veterinary Use (CVMP)
- Committee for Orphan Medicinal Products (COMP)
- Committee on Herbal Medicinal Products (HMPC)
- Committee for Advanced Therapies (CAT)
- Paediatric Committee (PDCO)
- Pharmacovigilance Risk Assessment Committee (PRAC).

Figure 1 – Opinions on human medicines adopted by the EMA between 1994 and 2014



Data source: EMA.

Since 1995, the EMA has recommended the authorisation of a total of 975 human medicines (see figure 1). It bases its opinions on the results of clinical trials conducted by the pharmaceutical companies: before a medicinal product is placed on the market and used in patients, it has to undergo investigation in humans with the aim of discovering or verifying the effects of the medicine in question (the 'investigational product'). Clinical trials are the responsibility of the Member State in which the trial takes place. The rules for conducting clinical trials in the EU are currently laid down in Directive 2001/20/EC, which will be replaced by Regulation EU No 536/2014 once it enters into force.

The main elements[18] of the Regulation are:

- a simplified application procedure;

[17] See the European experts list.

[18] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

- an EU portal and database for the registration of all clinical trials conducted in Europe;
- a single authorisation procedure for all clinical trials;
- reinforced transparency for clinical trials.

The European Clinical Trials Database (EudraCT),[19] managed by the EMA, contains data on all clinical trials conducted in the EU. A subset of the data is publicly accessible via the European Clinical Trials Register. Since 21 July 2014, sponsors are obliged to make the summary results of clinical trials publicly available.

On the basis of Regulation (EC) No 726/2004, the EMA issues a European public assessment report (EPAR) that contains the scientific conclusions of each evaluation it has carried out for all medicines, both those that were granted and those refused marketing authorisation. As required by the Regulation, a user-friendly summary is published together with the EPAR.

The EMA also gives scientific advice to pharmaceutical companies on the tests and studies they are required to perform, and guides them in their medicines development programmes. An example of the latter is the new pilot project on adaptive pathways (see point 5.1 below).

Within the framework of the EU pharmacovigilance system (see point 2.3 below), the EMA coordinates Member States' activities in connection with the monitoring of medicines for safety once placed on the market. Suspected adverse reactions reported by patients and health professionals, for instance, must be entered in the internet-based information system EudraVigilance[20] managed by the EMA.

In addition, the EMA coordinates Member States' supervisory activities. All manufacturers, importers and distributors of medicines require licences, which are entered in the EMA-operated database EudraGMDP. Manufacturers must undergo regular inspections, the results of which are also made public in the database (see points 4.1 to 4.3 on GMP, GDP and GVP).

The EMA charges the holders of marketing authorisations fees[21] for the services it provides, including its pharmacovigilance activities carried out at EU level.

Decisions on pricing or reimbursement of medicines do not fall within the remit of the EMA. These are taken at the level of each Member State, mainly in negotiations between governments and marketing authorisation holders.

Stakeholder participation in the activities of the Agency is explicitly mentioned in Recital 18 of Regulation (EC) No 726/2004 ('should establish and develop appropriate contacts with the parties concerned, in particular representatives of patients and health-care professionals'). The EMA has consequently created a network of more than 30 European patient and consumer organisations,[22] and established a Patients' and Consumers' Working Party. In addition, it has built up a network of over 20 organisations of healthcare professionals.[23]

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[19] See EudraCT.

[20] Eudravigilance currently holds around 4 million such reports.

[21] For a list of fees and the rules by which they are governed, see EMA webpage on fees payable.

[22] The terms of interaction are defined in the Revised framework for interaction between the European Medicines Agency and patients and consumers and their organisations.

[23] The terms of interaction are defined in the Framework for interaction between the European Medicines Agency and healthcare professionals.

EMA policy on the handling of conflicts of interest

The EMA faces the challenge of ensuring that the experts sitting on its scientific committees are free from financial or other interests. The Agency's revised policy on the matter entered into force on 30 January 2015. It takes into account the views of stakeholders – among them Parliament – expressed in a public workshop on 'Best expertise versus conflicts of interests: striking the right balance'.[24] In this context, the importance of the issue of conflicts of interest, and the need for transparent rules and an open debate, was clearly stressed.

2.2 Marketing authorisation procedures

European medicines legislation distinguishes[25] between **EU marketing authorisations** and **national marketing authorisations**.

EU authorisations are granted by the European Commission through the **centralised procedure** following an application to the EMA. For some medicines, this procedure is compulsory (see point 2.2.1. below).

National authorisations are granted by the Member States through the national competent authorities,[26] except for medicinal products that are authorised under Regulation (EC) No 726/2004. National authorisations for more than one Member State can be obtained through the **decentralised procedure** and the **mutual recognition procedure**.

The centralised, decentralised and mutual recognition procedures[27] are described below.

2.2.1 Centralised procedure

The centralised procedure, set up in 1995, is governed by Regulation (EC) No 726/2004 (in this section, referred to as 'the Regulation'). The Regulation introduces a single scientific assessment procedure of the highest standard for the medicinal products falling within its scope, with the aim 'to preserve the confidence of patients and the medical professions in the evaluation', especially in the context of new emerging therapies, and 'to ensure the effective operation of the internal market in the pharmaceutical sector'. The centralised procedure results in a single marketing authorisation that is valid in all Member States and offers, among other things, the benefit of direct access to the EU market.

The centralised procedure is mandatory[28] for:

- medicines containing a new active substance not authorised in the Community before 20 May 2004 (i.e. the date of entry into force of the Regulation) and that is intended for the treatment of acquired immune deficiency syndrome (AIDS), cancer, diabetes, neurodegenerative diseases, autoimmune disorders, as well as for viral diseases;

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[24] Report from the public workshop hosted by the European Medicines Agency in London on 6 September 2013.

[25] EudraLex – Volume 2A Procedures for marketing authorisation – Chapter 1 Marketing Authorisation, rev. 4, June 2013.

[26] List of the national competent authorities for human medicines.

[27] See also EMA webpage on the central authorisation of medicines, Commission webpage on the decentralised procedure, and Heads of Medicines Agencies webpage on the medicines approval system.

[28] According to Article 3(1) of the Regulation and its Annex.

- medicines derived from biotechnology processes, such as genetic engineering;
- advanced-therapy medicines, such as gene therapy and somatic cell therapy or tissue-engineered medicines (see point 3.4 below);
- orphan medicines (see point 3.1 below).

It is optional[29] for:

- medicines containing a new active substance not authorised before 20 May 2004, and intended for the treatment of diseases not listed above;
- medicines that constitute a significant therapeutic, scientific or technical innovation;
- medicines for which EU-level authorisation is in the interests of public health.

Under the centralised procedure, a company submits its application directly to the EMA, where it is assessed by the competent scientific committee (see point 2.1 above). After the evaluation (taking up to 210 days), the committee gives a recommendation (an 'opinion') on whether the medicinal product should be authorised or not. This opinion is then forwarded to the European Commission, which has the final say in the granting of marketing authorisations in the EU. After considering the opinion, the Commission can issue a legally binding EU-wide marketing authorisation. Once it is granted, the marketing authorisation holder can begin to market the medicine in the EU.

2.2.2 Decentralised procedure

The decentralised procedure is laid down in Directive 2001/83/EC (Chapter 4). It applies to medicines that have not yet been authorised in any Member State and are not eligible for the centralised procedure.

Under the decentralised procedure, a company that wants to market a medicinal product in more than one Member State, but does not want to use the centralised procedure, submits identical applications for marketing authorisation simultaneously to several Member States. It asks the Member State in which it wants to launch its product first to act as 'reference Member State'. The reference Member State carries out the initial evaluation and issues a draft assessment report. The other Member States in which the company has submitted applications (the 'concerned Member States') either agree with the evaluation or ask further questions. Once all issues are resolved and the application is successful, national marketing authorisations will be issued in the reference Member State and the other Member States concerned.

2.2.3 Mutual recognition procedure

The mutual recognition procedure is laid down in Directive 2001/83/EC. It is similar to the decentralised procedure: both procedures are based on the principle that Member States rely on each other's scientific evaluations, and mutually recognise existing national marketing authorisations. Unlike the decentralised procedure, mutual recognition applies to medicinal products that have already been authorised in a Member State.

Under the mutual recognition procedure, the reference Member State (here: the Member State that issued the original national marketing authorisation) submits its evaluation of the medicinal product to the concerned Member States (here: the other Member States in which the company wants to market its product). These are then asked to mutually recognise the marketing authorisation. If the applicant is successful, each Member State concerned will issue a national marketing authorisation. Should

[29] According to Article 3(2) of the Regulation.

any Member State refuse to recognise the original national authorisation on the grounds of a potential serious risk to public health, the matter is taken to the coordination group. It subsequently goes through various steps, including arbitration, and – if the Member States fail to reach an agreement – is ultimately referred to the Commission for decision.

2.3 Pharmacovigilance

Pharmacovigilance refers to the monitoring of the safety of medicines once they have been authorised and placed on the market (it is also termed 'post-authorisation supervision' or 'post-marketing surveillance').

Activities in the field of pharmacovigilance are geared towards the prevention, detection and assessment of any adverse reactions to medicines. This comprises the collection and evaluation of data, but also actions to protect the health of patients, including regulatory measures such as the introduction of the black triangle symbol (see box).

Pharmacovigilance activities are mainly implemented by the national competent authorities, the EMA and the European Commission, but rely on communication and exchange between all stakeholders: patients, health professionals, regulatory authorities and companies working in the pharmaceutical sector.

Pharmacovigilance is governed by:

- Regulation (EC) No 726/2004 as amended by Regulation (EU) No 1235/2010 (for centrally authorised medicinal products);
- Directive 2001/83/EC as amended by Directive 2010/84/EU (for nationally authorised medicinal products including those authorised through the decentralised and mutual recognition procedures);
- Commission Implementing Regulation (EU) No 520/2012.[30]

Black triangle

Since 1 September 2014, a black inverted triangle must be printed on the package leaflet of medicines that are being monitored particularly closely. It is intended to help patients and healthcare professionals identify the medicines concerned, and to encourage them to report any suspected side effects from the use of these medicines. The views of patients and healthcare stakeholders were taken on board in formulating the recommendation to introduce the black triangle.

This body of legislation was the result of a major revision undertaken to rationalise the pharmacovigilance system, particularly with a view to eliminating obstacles to the free movement of medicines. The revision also aimed to strengthen public health through improved prevention, detection and assessment of adverse reactions. The new provisions introduce the possibility for patients to report adverse drug reactions directly to the national competent authorities, and expressly encourage them to do so. Moreover, the scope of reporting was widened to include medication errors and overdose.

The legislation also established a new scientific committee at the EMA, the Pharmacovigilance Risk Assessment Committee, and provided for further development of the pharmacovigilance database established in 2004 (now renamed Eudravigilance): the database should be equipped to immediately forward reports on suspected adverse

[30] Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council.

reactions from marketing authorisation holders to the Member States on whose territory the reaction occurred, and become a single point for reception of such information.

Since then, pharmacovigilance incidents in the EU have prompted a requirement to further strengthen the new legislation. That led to the adoption of:

- Directive 2012/26/EU[31] and Regulation 2012/1027/EU[32] (applicable since June and October 2013), which, respectively, require a notification to the national competent authorities when a medicine is withdrawn, and address information requirements, such as a list of medicinal products that are subject to additional monitoring;
- Implementing Regulation No 198/2013[33] (since March 2012), which introduces the black triangle;
- Commission Delegated Regulation (EU) No 357/2014,[34] which empowers the EMA or the Commission to require a post-authorisation efficacy study in certain cases.

2.4 Special procedures

2.4.1 Article 58 applications for use in third countries

The procedure for Article 58 applications[35] applies for medicines that are intended exclusively for use in countries outside the EU, so as to allow rapid access to medicines in these countries.

Medicines are eligible for this procedure if they are used to prevent or treat diseases of major public health interest. These include,[36] among others:

- vaccines used in the Expanded Programme on Immunisation (EPI) of the World Health Organization (WHO);[37]
- vaccines for protection against a public health priority disease;
- medicines for WHO target diseases such as HIV/AIDS, malaria or tuberculosis.

Under this procedure, the EMA's Committee for Medicinal Products for Human Use (CHMP) gives scientific assistance in cooperation with WHO. The CHMP carries out the scientific assessment and, after consultation with WHO, adopts an opinion. For all positive opinions adopted under Article 58, the EMA publishes an EPAR.

2.4.2 Compassionate use

The compassionate use procedure is laid down in Article 83 of Regulation (EC) No 726/2004. It refers to the use of an unauthorised medicinal product under limited

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31 Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance of the Council.

32 Regulation (EU) No 1027/2012 of the European Parliament and of the Council of 25 October 2012 amending Regulation (EC) No 726/2004 as regards pharmacovigilance.

33 Commission Implementing Regulation (EU) No 198/2013 of 7 March 2013 on the selection of a symbol for the purpose of identifying medicinal products for human use subject to additional monitoring.

34 Commission Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required.

35 See EMA webpage on Article 58 applications.

36 Committee for Medicinal Products for Human Use (CHMP) Guideline on procedural aspects regarding a CHMP scientific opinion in the context of cooperation with the World Health Organization (WHO) for the evaluation of medicinal products intended exclusively for markets outside the Community.

37 See WHO webpage on national programmes and systems.

and strictly controlled conditions to allow certain patients earlier access to medicines. The concept goes back to Directive 2001/83/EC: Member States can make national arrangements for health professionals to commission the manufacture of an unauthorised medicine to fulfil the 'special needs' of a patient under their 'direct personal responsibility'.

Compassionate use is eligible for patients:

- who have a chronically or seriously debilitating disease;
- whose disease is considered life-threatening;
- who cannot be treated satisfactorily by an authorised medicinal product or cannot enrol in a clinical trial.

Compassionate use programmes are often managed by the Member States, which decide according to national legislation whom to include. The CHMP can play a complimentary role by favouring a common, standardised approach towards compassionate use programmes across the EU. It can give non-binding recommendations to EU Member States on how to administer, distribute and use medicines for compassionate use, and to identify those patients who may benefit from such programmes.

3 Regulatory rules for specific types of medicinal products

A number of medicines for particular uses and/or groups of patients are governed by specific rules. These are described in more detail below.

3.1 Orphan medicines

Orphan medicinal products are covered by Regulation (EC) No 141/2000[38] and its Implementing Regulation.[39]

Orphan medicines (i.e. medicines for rare diseases), are medicinal products for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 000 persons in the EU. Most orphan diseases[40] are genetic.

The Regulation is underpinned by a threefold economic, epidemiological and ethical rationale: because some conditions occur so infrequently, the pharmaceutical industry lacks the financial interest to develop medicines for them, under normal market conditions; patients suffering from a rare disease should, however, be entitled to the same quality of treatment as other patients. To ensure access to treatment for those patients, the EU therefore seeks to stimulate research, marketing and development of orphan medicinal products and to provide incentives to the sponsor. These include a

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[38] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

[39] Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts 'similar medicinal product' and 'clinical superiority'.

[40] A comprehensive list of orphan diseases can be found on Orphanet, the reference portal for information on rare diseases and orphan drugs, which is jointly financed by Inserm (the French National Institute of Health and Medical Research), the French Directorate General for Health and the European Commission.

ten-year period of market exclusivity after the medicine is authorised, protocol assistance and the possibility to request reductions in EMA fees.

The Regulation also establishes a centralised procedure for the designation of orphan medicines, and sets up a Committee for Orphan Medicinal Products that is responsible for the scientific assessment of orphan-medicine applications.

To date, the European Commission has authorised 111 orphan medicinal products,[41] and 1 105 products have been designated as orphan medicines.

3.2 Paediatric medicines

Medicinal products for paediatric use (i.e. medicines for use in children) are governed by Regulation (EC) No 1901/2006.[42]

The Regulation sets up requirements, rewards and incentives to:

- facilitate the development and accessibility of medicines for babies and children aged up to 17 years old;
- ensure that those medicines are ethically researched, of high quality and appropriately authorised for use in children;
- improve the information on the use of paediatric medicines.

These aims should be achieved without subjecting children to unnecessary clinical trials or delaying the authorisation of medicinal products for adults.

The Regulation also sets up a Paediatric Committee, which is responsible for giving opinions on medicines for use in children.

The Regulation is seen as bridging a gap, namely the lack of a sufficient number of suitable, authorised medicines for treating children: as pharmaceutical companies frequently have not conducted sufficient research and development to meet the specific therapeutic needs of children.

Since the Regulation came into force, there has been some follow-up. In June 2013, the European Commission presented a progress report[43] on the first five years of its application. Looking at the experience gained, including the results of a public consultation, the report finds that the development of paediatric medicines has become an 'integral part of the overall development' of medicinal products, and that the Regulation works as a 'catalyst to improve the situation of young patients'. In September 2014, a new guideline[44] on applications for paediatric investigation plans under the Regulation was published.

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41 For a complete list of orphan medicinal products authorised in the EU, see the Community Register.

42 Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, and Regulation (EC) No 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending Regulation 1901/2006 on medicinal products for paediatric use.

43 European Commission, Better Medicines for Children – From Concept to Reality, Progress Report on the Paediatric Regulation (EC) No 1901/2006.

44 Communication from the Commission — Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies.

3.3 Geriatric medicines

There is no specific EU pharmaceutical legislation covering medicinal products for geriatric use (i.e. medicines for older people, aged 65 years or over). They are, however, the focus of a geriatric medicines strategy[45] published by the EMA in 2011. The strategy is the result of the Agency's engagement with regulatory authorities, pharmaceutical companies and stakeholder organisations. It is based on EMA recognition that, as the number of older people in the EU increases, the development, approval and use of medicines would have to take into account their specific needs. These needs arise from the fact that older people:

- metabolise medicines differently;
- are at risk of developing a wide range of diseases, including Alzheimer's, heart disease and mental illness;
- often have more than one illness at the same time;
- may be weaker and more vulnerable to the risks of medical treatment than younger patients.

The EMA's strategy aims to:

- ensure that medicines for older people are of high quality and that they are appropriately researched and evaluated for use in this population, both before and after they are authorised;
- improve the availability of information on the use of geriatric medicines.

As part of the strategy, the EMA produces scientific guidelines to help companies conduct studies, and is developing guidance on packaging and formulations.

The Agency's CHMP has also established an expert group[46] on issues related to older people.

3.4 Advanced-therapy medicines

Advanced-therapy medicinal products (ATMPs) are governed by Regulation (EC) No 1394/2007[47] (the ATMP Regulation). ATMPs are novel biotechnology medicines based on cells and tissues. They comprise:

- gene therapy medicinal products;
- somatic-cell therapy medicinal products;
- tissue-engineered products;
- combined advanced-therapy products.

The Regulation aims to address the complexity and specific character of ATMPs. It:

- clarifies their definition;
- establishes specific technical requirements;
- stipulates that they must be regulated under the centralised marketing authorisation procedure so they can benefit from EU-level expertise;

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45 EMA geriatric medicines strategy, 17 February 2011.

46 Geriatric Expert Group (GEG).

47 Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.

- sets up a multidisciplinary Committee for Advanced Therapies at the EMA for their assessment.

Gene therapy medicinal and somatic-cell therapy medicinal products were already defined in Annex I to Directive 2001/83/EC. Gene therapy medicines contain genes that have a therapeutic effect and work by inserting recombinant genes into cells. Somatic-cell therapy medicines contain, or consist of, cells or tissues that have been manipulated to change their biological characteristics.

Tissue-engineered products and combined advanced-therapy products are defined for the first time in the ATMP Regulation. Tissue-engineered medicines contain cells or tissues that have been modified so they can be used to repair, regenerate or replace tissue. Combined advanced-therapy medicines may consist of a combination of biological materials ('viable materials') and chemical structures ('non-viable materials'). If their principal mode of action is pharmacological, immunological or metabolic, they fall within the definition of ATMP.

In addition to its technical elements, the Regulation also comprises an economic dimension, namely:

- to ensure the free movement of ATMPs within the EU, facilitate their market access and foster the competitiveness of the European biotechnology sector;
- to give special incentives for small and medium-sized enterprises (SMEs), bearing in mind that the economic operators involved are not large pharmaceutical companies, but small businesses or hospitals.

In 2012, the Commission undertook a public consultation on the application and impact of the ATMP Regulation. The results were published in a report[48] in April 2014. It concludes that, despite the big potential benefits of these therapies for patients, there are still many unknown elements, which is why adequate controls are necessary to prevent negative consequences for public health.

3.5 Herbal medicines

The provisions for herbal medicinal products are laid down in Directive 2004/24/EC[49] (the Traditional Herbal Medicinal Products Directive, THMPD) amending Directive 2001/83/EC. Herbal medicines contain herbal (i.e. plant-derived) substances as active ingredients. Some of these are very potent and potentially dangerous for patients. To ensure the safety, efficacy and quality of herbal medicines, and to remove differences and uncertainties about their status in the different Member States, the EU decided to place them under EU pharmaceutical legislation.

The Directive introduces a simplified EU-wide authorisation, or 'registration'. It sets out a transition period that ended on 30 April 2011: products that were placed on the market before the Directive came into force could continue to be marketed under traditional national rules until the transition period expired; from 1 May 2011, an EU marketing authorisation is required.

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[48] Report from the Commission to the European Parliament and the Council in accordance with Article 25 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004.

[49] Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use.

'Household names' now regulated

The list of herbal substances for registration contains some well-known traditional remedies such as:

- *Arnica*
- *Calendula*
- *Echinacea*
- Lavender
- Thyme
- Valerian.

The Directive distinguishes between herbal medicines for 'traditional use' and those with 'well-established medicinal use'. Medicines for traditional use are those with a long tradition that do not fulfil the requirements for a marketing authorisation, i.e. that the applicant can 'demonstrate by detailed references to published scientific literature that ... the constituents of the medicinal products ... have a well-established medicinal use with recognised efficacy and an acceptable level of safety'. The simplified registration procedure (or 'traditional-use registration') applies to medicines for traditional use. Applications for registration have to fulfil the same quality and safety requirements as applications for a marketing authorisation, but they do not have to prove efficacy – the traditional indications must simply be 'plausible'.

The three different application routes are:

- traditional-use application: on the basis of sufficient safety data and plausible efficacy, after having been in use for at least 30 years, including at least 15 years in the EU; the medicine is granted a traditional-use registration (simplified registration procedure) by a Member State;
- well-established use application: demonstrated by means of scientific literature establishing that the active substances of the medicinal products have been in well-established medicinal use within the EU for at least ten years, with recognised efficacy and an acceptable level of safety; the medicine is granted a marketing authorisation by a Member State or via an application to the EMA;
- stand-alone application/mixed application: evaluation of an application consisting only of safety and efficacy data from the company's own development (stand-alone application) or a combination of own studies and bibliographic data (mixed application); the medicine is granted a marketing authorisation by a Member State or via application to the EMA.

Because of the particularities of herbal medicinal products, a Committee for Herbal Medicinal Products has been established at the EMA. It prepares Community herbal monographs[50] that contain information on what a particular herbal medicine is used for and who it is intended for, as well as on its effects and interactions.

To facilitate the registration, a list of herbal substances and preparations has been established on the basis of Commission Decision 2008/911/EC,[51] which has been amended several times through Implementing Decisions.

3.6 Homeopathic medicines

The provisions for homeopathic medicinal products are laid down in Directive 2001/83/EC. Homeopathic medicines are medicinal products prepared from substances known as homeopathic stocks in accordance with a manufacturing procedure described

[50] See also the database on herbal medicines for human use.

[51] Commission Decision of 21 November 2008 establishing of a list of herbal substances, preparations and combinations thereof for use in traditional herbal medicinal products (notified under document number C(2008) 6933).

in the European Pharmacopoeia (or in the official pharmacopoeia of a Member State). They contain very low levels of diluted active principles.

Homeopathic medicines are authorised by the medicines regulatory authorities in each Member State. The national regulatory regimes vary greatly. While some Member States recognise homeopathy by law as a therapeutic system, others have no such regulation.[52] The Directive therefore aims to harmonise the rules for manufacture, control and inspection to allow the circulation of homeopathic medicines that are safe and produced to quality standards. It also introduces a special, simplified registration procedure that takes into account their particular characteristics.

Homeopathic medicines are eligible for the simplified procedure on the condition that:

- they are administered orally or externally (i.e. not by injection, for instance);
- no specific therapeutic indication appears on the labelling or in the patient information;
- they present a sufficient degree of dilution to guarantee the safety of the medicinal product.

The Heads of Agencies have established a Homeopathic Medicinal Products Working Group (HMPWG)[53] as a forum for exchange of expertise, and to provide guidance on the assessment of homeopathic medicines and on their registration.

Traditional herbal and homeopathic medicines: a choice

Parliament's Intergroup for Complementary and Alternative Medicine (CAM) organised a joint meeting on the subject in June 2013. In his speech, then-Health Commissioner Tonio Borg stressed that patients 'should have access to the medicinal products of their choice', including traditional herbal and homeopathic medicines. All measures had to be taken to ensure the quality, safety and efficacy of such medicines by means of a 'less burdensome' procedure than that required by the full marketing authorisation.

3.7 Non-prescription medicines

Non-prescription medicinal products are covered by Directive 2001/83/EC. They are also referred to as OTCs (over-the-counter medicines) as they can be purchased without a medical prescription.

The Directive contains a negative definition of non-prescription medicines as medicinal products that do *not* meet the criteria listed in Article 71 of the Directive (i.e. the criteria for prescription-only medicines):

- *likely to present a danger either directly or indirectly, even when used correctly, if utilised without medical supervision, or*
- *frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health, or*
- *contain substances or preparations thereof, the activity and/or adverse reactions of which require further investigation, or*
- *normally prescribed by a doctor to be administered parenterally* [by injection].

When a marketing authorisation is granted, the medicine regulatory authorities of the Member States must specify if the medicinal product is to be classified as non-

[52] Information on the current regulatory status of homeopathy in the different EU Member States can be found on the ECH webpage on ECH in European countries.

[53] See Homeopathic Medicinal Products Working Group (HMPWG).

prescription medicine on their territory. In the light of 'new facts', they can subsequently change the legal status from prescription to non-prescription. This reclassification, or 'switch', is addressed in Article 74 of the Directive and explained in a guideline.[54]

4 Instruments for guaranteeing the quality, integrity and safe use of medicinal products

Directive 2001/83/EC sets out which documents have to be provided in an application for marketing authorisation. These documents have to show that the medicinal product in question fulfils the legal requirements in terms of quality, safety or efficacy. Annex 1 specifies these requirements and mentions two sets of guidelines that must be applied: the European Commission's pharmaceutical guidelines published in the different volumes of 'The rules governing medicinal products in the EU', and the scientific guidelines[55] prepared by the Committee for Medicinal Products for Human Use (CHMP) at the EMA, in consultation with the national medicines regulatory authorities. They aim to ensure harmonised application of requirements across the EU through a set of tools, such as the principles of GMP, GDP and GVP. These are described below.

4.1 Good manufacturing practice (GMP)

Good manufacturing practice is laid down in Directive 2001/83/EC, which – based on Article 47 – provides for a Directive[56] and detailed guidance.[57] GMP is defined as the part of quality assurance that guarantees 'that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use'.[58] In addition, the EMA operates EudraGMDP,[59] a database that contains information on manufacturing and import authorisations, GMP certificates, statements of non-compliance with GMP, and GMP-inspection planning in third countries.

A company that wants to manufacture a medicinal product in the EU must hold a manufacturing authorisation. Moreover, all medicinal products for human use in the EU must be manufactured according to the principles and guidelines of GMP. These comprise criteria referring to quality management, personnel, premises and equipment, documentation, production, quality control, contracting out, complaints and product recall, and self-inspection. These provisions also apply to medicines intended for export, as well as to medicines and active substances imported into the EU. According to the Directive, active substances must be accompanied by a written confirmation from the competent authority of the exporting third country that the GMP standards in the manufacturing site are equivalent to those of the EU. Should this not be the case, a statement of non-compliance (NCS) is issued and entered in EudraGMDP. The EU then takes measures to prevent the active substances produced at this particular site being used in the EU.

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54 European Commission, Enterprise and Industry Directorate-General, A guideline on changing the classification for the supply of a medicinal product for human use, rev. January 2006.

55 EudraLex – Volume 3 Scientific guidelines for medicinal products for human use.

56 Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use.

57 EudraLex – Volume 4 Good manufacturing practice.

58 Commission Directive 2003/94/EC.

59 The creation of EudraGMDP is referred to in Article 111(6) of Directive 2001/83/EC.

4.2 Good distribution practice (GDP)

Good distribution practice is also laid down in Directive 2001/83/EC and specified in periodically updated Commission guidelines[60] based on Article 84 and Article 85b(3). According to these guidelines, GDP is 'that part of quality assurance that ensures that the quality of medicinal products is maintained throughout all stages of the supply chain from the site of manufacture to the pharmacy or person authorised or entitled to supply medicinal products to the public'. All wholesale distributors must hold a distribution authorisation and comply with the GDP principles and guidelines. The guidelines on GDP contain similar criteria to those on GMP, but additionally cover measures to avoid suspected falsified medicinal products from entering the EU supply chain.

4.3 Good pharmacovigilance practice (GVP)

To support the implementation of the pharmacovigilance legislation (see point 2.3 above), the EMA has developed several modules of guidelines[61] on good pharmacovigilance practice that aim to facilitate pharmacovigilance activities in the EU. GVP covers centrally authorised medicines as well as nationally authorised medicines. It applies to marketing authorisation holders, the EMA and the national medicines regulatory authorities.

4.4 Information to patients

Patients have to be properly informed about medicines. Given the vast amounts of information readily available through different channels, the EU has deemed it necessary to ensure access to information that is accurate, objective, reliable, substantiated by evidence, up-to-date and of high quality.

4.4.1 Legislative approach

The regulatory basis for patient information is Directive 2001/83/EC. Medicinal products must be accompanied by labelling and package leaflet information that is easily legible, clearly comprehensible and also appropriate for the blind (in Braille). This information must be drafted in consultation with patient groups. Guidance[62] has been developed to achieve readability.

Regulation (EC) No 726/2004 introduced a number of further criteria in regard to patient information, such as:

- the requirement to publish a public assessment report (EPAR), including a user-friendly summary of product characteristics;
- the basis for access to information on pharmacovigilance and clinical trials;
- the creation of a database on medicinal products accessible to the general public (EudraPharm).[63]

In the framework of the 2008 pharmaceutical package, attempts were made to harmonise rules on the provision of information about medicines to patients across the

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[60] Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use, 2013/C 343/01.

[61] See EMA webpage on good pharmacovigilance practices.

[62] Guideline on the readability of the labelling and package leaflet of medicinal products for human use, rev. 1, 12 January 2009.

[63] EudraPharm.

EU and to ensure equal access to reliable information on the medicines available. However, the Commission withdrew its two proposals in May 2014.

4.4.2 Non-legislative approach

To optimise the quality of the information – the summary of product characteristics, labelling and package leaflet – a company is legally obliged to provide to the public, the EMA has created annotated product-information templates[64] for applicants. The Working Group on Quality Review of Documents[65] reviews these templates. It also assists the scientific committees with linguistic aspects, to ensure the clarity, consistency and readability of the information.

4.5 Protection against falsified medicines

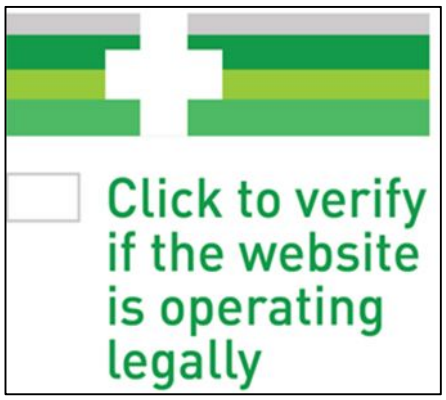
The legal basis for preventing falsified medicinal products from entering the EU supply chain is Directive 2001/83/EC as amended by Directive 2011/62/EU, which adds relevant provisions.

Falsified medicinal products are 'fake' medicines as regards their identity, history or use. They usually contain sub-standard or falsified active substances and pose a major threat to public health. (The term 'falsified' is used to distinguish them from 'counterfeit' medicines, which violate intellectual property rights.)

The new legislation introduces stricter rules to ensure that medicines are safe and that the trade in medicines is rigorously controlled. These include:

- a common, EU-wide logo to identify legal online pharmacies, which has to be clearly displayed on every page of the website offering the medicine[66] (see figure 2);
- an obligation to ensure that manufacturers comply with GMP for active substances, including stricter controls and inspections;[67]
- EU-wide rules on the import of active substances;[68]
- an obligatory safety feature ('unique identifier' such as a barcode) on the outer packaging of medicines to verify the authenticity of a medicinal product (to be specified in a delegated act).

Figure 2 – EU-wide logo for identifying legal online pharmacies



Data source: European Commission.

[64] See EMA webpage on product-information templates.

[65] See EMA webpage on the Working Group on Quality Review of Documents.

[66] Commission Implementing Regulation (EU) No 699/2014 of 24 June 2014 on the design of the common logo to identify persons offering medicinal products for sale at a distance to the public and the technical, electronic and cryptographic requirements for verification of its authenticity.

[67] Commission Delegated Regulation (EU) No 1252/2014 of 28 May 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council with regard to principles and guidelines of good manufacturing practice for active substances for medicinal products for human use.

[68] Commission Implementing Decision of 23 January 2013 on the assessment of a third country's regulatory framework applicable to active substances of medicinal products for human use and of the respective control and enforcement activities pursuant to Article 111b of Directive 2001/83/EC of the European Parliament and of the Council.

Some stakeholders[69] look back at 50 years of EU medicines legislation

For the European Federation of Pharmaceutical Industries and Associations, the creation of the European Medicines Agency was a real milestone in EU pharmaceutical legislation.

GIRP, the European association of pharmaceutical full-line wholesalers, applauds the increase in quality, safety and efficacy standards for medicines, but asks for 'smart legislation' to avoid disproportionate administrative burdens on the medicines supply chain.

The European Patients' Forum welcomes 'the advances in recent years towards meaningful patient involvement in medicines safety, exemplified by the European Medicines Agency model' with its centralised medicines assessment.

BEUC, the European consumer organisation, considers that EU pharmaceutical legislation has over the last 50 years contributed to making sure that disasters such as the thalidomide tragedy would not occur again. In its view, the current framework 'strikes the right balance between thorough pre-market assessment and timely access to treatment for patients'.

5 A glimpse into the near future

5.1 The 'adaptive pathways' approach as a means to improve timely access to new medicines

Currently, there is some discussion of 'adaptive pathways', also known as 'progressive licensing' and 'staggered approval', a concept that stands for progressive access to medicines before their full authorisation, in particular for patients who have a medical condition that is not addressed adequately by an existing therapy (i.e. an 'unmet medical need'). This starts with early authorisation of a new medicine for a specific, restricted subgroup of patients – particularly those with life-threatening, severely debilitating or very rare conditions for which there is no adequate treatment available. The adaptive pathways approach consists of two scenarios: one, a medicine is initially approved for a well-defined, restricted subset of patients before full market authorisation, and its indication is then progressively expanded to a wider patient population. Two, following early approval, the risk/benefit of the medicine is continuously re-assessed as new evidence on its use in patients is gathered.

The adaptive pathways approach builds on EU regulatory procedures already in place, such as the centralised procedure for compassionate use (see also 2.4.2).

The EMA is currently running a pilot project[70] on adaptive licensing. It started in March 2014 with the EMA inviting companies to participate. They were asked to submit ongoing medicines-development programmes for consideration as prospective pilot cases. Only experimental medicines in the early stages of clinical development were considered. In December 2014, the EMA published a report on the initial experience and the next steps. By then, it had received and assessed 34 applications, ten of which were selected for discussion with the applicant. Stage I of the pilot ended on 28 February 2015; Stage II will include in-depth meetings with selected applicants.

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[69] Stakeholder quotes cited from 'Users want more after 50 years of EU pharmaceutical rules', *European Voice*, 10 February 2015.

[70] See EMA webpage on adaptive pathways.

The authors of a dedicated analysis[71] identified, among others, the following main drivers for adaptive pathways.

- Patients demand timely access to medicines, and with adaptive pathways, some severely ill patients could benefit from new treatments earlier.
- A better understanding of pathologies has allowed the identification of subgroups of patients who may better respond to certain medicines than others. For them, adaptive licensing may be the only option to access new medicines.
- Healthcare systems are under a growing financial burden, and there are calls for more targeted use of medicines, to increase their therapeutic value.
- The pharmaceutical industry is under pressure to make the development of medicines sustainable, and medicines development programmes that target specific well-defined, smaller patient populations would facilitate financing and allow for marketing of more medicines.

The European Commission has recently set up an expert group within its pharmaceutical committee, the Group on Safe and Timely Access to Medicines for Patients (STAMP).[72] STAMP aims to find ways to improve safe and timely access to medicines by using the existing EU regulatory tools more effectively. This has triggered reactions and expectations on the part of stakeholders, including the following.

Adaptive pathways: stakeholder reactions and expectations

The European Federation of Pharmaceutical Industries and Associations (EFPIA) calls for the creation of 'the framework required to successfully implement "Medicines Adaptive Pathways for Patients" (MAPP) as a basis for introducing new treatments for selected populations'.[73] In EFPIA's view,[74] the successful implementation of the model presupposes that regulators, authorities, payers, health professionals, patients and industry fully understand its value. Among the current challenges for EFPIA are getting all stakeholders to agree on the evidence that is required, and that they be willing to work in a context of increased uncertainty.

The European AIDS Treatment Group (EATG) and the European Liver Patients Association (ELPA) organised a multi-stakeholder meeting[75] on early access to new medicines for treating hepatitis C. The question of participation in early access programmes was raised, and the criteria for inclusion (for instance in the case of prisoners). Another issue mentioned was that of the financing of these programmes – who pays, the government or the pharmaceutical companies? It was also suggested that companies might use such programmes as pre-marketing tools.

EURORDIS, a patient organisation active in the field of rare diseases, advocates what it calls 'progressive patient access'.[76] It considers this a means to accelerate access to 'more safe, effective and affordable innovative therapies with real therapeutic added-value for rare-disease patients in the EU'.

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71 Eichler, H.-G. et al. (2015), 'From adaptive licensing to adaptive pathways: Delivering a flexible life-span approach to bring new drugs to patients', *Clinical Pharmacology & Therapeutics,* doi: 10.1002/cpt.59.

72 STAMP held its first meeting on 27 January 2015.

73 EFPIA: The right prevention and treatment for the right patient at the right time. Strategic Research Agenda for Innovative Medicines Initiative 2, 25 March 2014.

74 See EFPIA webpage on MAPPs.

75 'Pathways to provide access to novel HCV compounds to people for whom they are yet not authorised, but who have no alternative treatments', Meeting report, International multi-stakeholder meeting, 19-20 June 2013, Brussels.

76 EURORDIS: Promotion of Progressive Patient Access bears fruit, 11 June 2014.

6 Further reading

European Parliament Factsheets on the European Union – Medicines and medical devices.

European Commission Public health portal, notably the website on Medicinal products for human use and its dedicated webpages.

European Medicines Agency portal, notably the website on Human medicines: regulatory information and its dedicated webpages.

EU legislation on human medicines goes back 50 years. Its twofold aim is to safeguard public health without hindering development of the European pharmaceutical industry or trade in medicinal products. The regulatory framework is complex and covers the entire lifecycle of a medicine, from manufacture, to clinical trials, to marketing authorisation, to pharmacovigilance and patient information. Added to that, the principles of good manufacturing, distribution and pharmacovigilance practice contribute to increasing medicines' safety. An emerging approach to granting early access to medicines – adaptive pathways – could prove its future merits for patients with a medical condition not adequately addressed by an existing therapy.

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