
GENERAL

**LEGAL INSTRUMENTS SUPPORTING THE DEVELOPMENT OF ORPHAN
MEDICINAL PRODUCTS IN THE EUROPEAN UNION****KATARZYNA MIASKOWSKA-DASZKIEWICZ***

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Abstract: Securing the freedoms of the Internal Market by the European Union entails an obligation to implement such mechanisms so that medicinal products placed on the market could be, on the one hand, widely available to the citizens of Member States and, on the other, so that medicinal products could be both safe and effective. The first aspect involves acting towards the improvement of public health and the prevention of human diseases and troubles, while the second – removing the sources of danger to human health. From this perspective, we need to highlight the problem of a deficit in the development, and thus a deficit in the availability of medicinal products authorized for marketing, which are intended for use in rare diseases. This paper aims to analyze the European Union pharmaceutical law in order to establish whether, and if yes – how the EU legal regulations support the development and availability of orphan medicinal products on the Internal Market.

Keywords: orphan medicinal product, rare disorders, marketing authorization, industrial property rights

Considering the protection of public health, the European law establishes a rule that no medicinal product can remain on the market without a valid authorization issued by an appropriate authority. Depending on which authority issues the authorization, one can distinguish between a national procedure: the authorization is issued by an administrative authority of a Member State (in Poland, since 1 May 2011 it is the President of the Office for Registration of Medicinal Products, Medical Devices and Biocids) or a central procedure: the regulator is the European Union, which resolves disputes on the basis of an evaluation report of the European Medicines Agency. The basic EU regulation in this respect is the Directive of the European Parliament and of the Council 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28. 11. 2001, p. 67 (hereinafter Directive 2001/83/EC), along with its most important revision – the Directive of the European Parliament and Council 2004/27/EC of 31 March 2004 (OJ L 136, 30. 04. 2004, p. 1; hereinafter Directive 2004/27/EC), as well as the

Regulation (EC) 726/2004/EC of 31 March 2004, laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30. 04. 2004, p. 1; hereinafter Regulation (EC) 726/2004/EC).

The marketing authorization of medicinal products is performed on the basis of an appropriate administrative procedure and an application that meets detailed criteria. Marketing authorization for a medicinal product is issued on the basis of an evaluation of the product's safety, its therapeutic efficacy and quality.

The protection of health plays a significant role in the policy of the EU; it is a part of many areas of the *acquis*, and its realization, according to the Treaty on the Functioning of the European Union (hereinafter referred to as TFEU), is multi-sectoral. This means analyzing each EU policy with regard to the realization of health protection, which has the highest priority according to Art. 168 of the TFEU. The principle indicated in the cited Treaty provision is sometimes described as a 'cross-section clause' as its content can be defined as an order, formulated in

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a positive manner, extracted from the entire activity of the European Union (1).

The specificity of the orphan medicinal products on the market

The notion of an “orphan drug” was first used in 1983 to describe treatment recommended to patients with rare diseases. That year, the United States of America announced the *Orphan Drug Act* (2). The law aimed at creating favorable conditions for the research and development of “orphan drugs” used in the treatment of rare diseases.

The Community programme for rare diseases, including genetic ones, defines the frequency of rare diseases as affecting no more than 5 of every 10,000 people in the EU (3). Regardless of the fact that rare diseases occur infrequently, the total number of people affected with such diseases in the EU ranges from 27 to 36 million. Most cases concern diseases that occur rarely and affect a maximum of 1 per 100,000 people (4). From the point of view of large pharmaceutical companies, orphan drugs are hardly profitable as they are intended for a small number of patients, i.e., finally, for a small percentage of purchasers. Therefore, one faces a dilemma: on the one hand, the number of recipients is insufficient to consider manufacture as profitable but on the other, these medicines are often the only possibility to save patients’ life and health. Thus, orphan drugs remain products developed mostly by small, innovative laboratories, generally remaining of little interest to the global pharmaceutical companies.

If the principal reason behind this is the limited market of consumers, other reasons should not be overlooked. They include the necessity of conducting long-lasting and costly preclinical tests and clinical trials, undergoing a marketing authorization procedure with hardly any guarantee of market success. We may also add to this list of obstacles the lack of infrastructure necessary to conduct research on the development of innovative orphan medicinal products.

The phenomena cited above are the reasons of why products that have never been tested for their safety and therapeutic efficacy for these indications are used in the therapy of rare diseases, leading in turn to the popularization of medicinal products used in an “off-label” (unapproved) manner.

Apart from the obvious medical doubts, the use of off-label medicinal products entails problems related to the responsibility of doctors who use them in a therapy. Prescribing medicinal products should be considered a health care service within the meaning of Article 3(a) of Directive 2011/24/EU of

the European Parliament and of the Council of 9 March 2011 on the application of patients’ rights in cross-border healthcare (OJ L88, 4. 04. 2011, p. 45–65).

The doctor’s decision to use an off-label medicinal product also involves administrative and financial problems with regard to the possibility of reimbursing a therapy conducted with the use of an off-label medicinal product.

In view of this situation, the need to create legal instruments which will support the development of orphan medicinal products is highly important.

The concept of stimulating the development and thus increasing the availability of orphan medicinal products is based on the introduction of changes to the procedure of their authorization for marketing in the European Union and on the creation of an incentive system for the pharmaceutical sector.

The normative activity of the European Union in the field of orphan medicinal products

The *ratio legis* of the Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22. 01. 2000, p. 1–5) is based on the assumption that patients suffering from rare conditions should have the right to the same quality of treatment as other patients, and thus it is necessary to support the research and development and subsequent marketing of appropriate medicines by the pharmaceutical industry. An additional stimulus was the fact that incentives for the development of orphan medicinal products have been successful in the United States of America since 1983, and in Japan since 1993.

The European Parliament and the Council eventually adopted Decision 1295/1999/EC of 29 April 1999 adopting a programme of Community action on rare diseases within the framework for action in the field of public health (1999 to 2003; OJ L 155, 22. 06. 1999). This included legislation aimed at the provision of information, the handling of rare disease clusters within the population, and the support of appropriate patient organizations. In the White Paper “Together for Health: A Strategic Approach for the EU 2008–2013” of 23 October 2007, presenting the EU health strategy, the Commission pointed out rare diseases as one of its priorities for action (SEC(2007) 1374-1376).

The strategy selected by the EU for improving the availability of medicinal products intended for rare diseases is also important. Considering the

principle of competence division between Member States and the European Union (Art. 4(1) in connection with Art. 2(2) of the TFEU), and the related principle of subsidiarity, it was concluded that due to the small ratio, specific character and yet high total number of affected people, the problem of rare diseases needs to be solved at the EU level. This explains why the chosen form was a regulation: it is binding in its entirety and directly applicable in all Member States (Art. 288 of the TFEU).

Designation of a medicinal product as an orphan medicinal product

For the easy and unambiguous identification of medicinal products subject to incentives, an open and clear EU procedure allowing for the designation of potential medicinal products as orphan medicinal products was established.

Article 2(b) of Regulation (EC) No. 141/2000 introduces a definition of an orphan medicinal product, the criteria of which are based on the prevalence of the condition for which the means of diagnosis, prevention or treatment are sought. A medicinal product can be designated as an “orphan drug”, in accordance with Article 3 of Regulation (EC) No. 141/2000, if its sponsor can establish a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the EU when the application is made, or that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the medicinal product in the EU would generate sufficient return to justify the necessary investment, and b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

The notion of sponsor also requires explanation. Article 2(c) of Regulation (EC) No. 141/2000 provides that a “sponsor” means any legal or natural person, established in the European Union, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product. The scope of entities included in the notion of a “sponsor” is thus fairly broad as it covers entrepreneurs who have their registered offices outside of the EU, whilst it is sufficient for them to run their business on the EU territory in the form of a branch.

Particular attention should be paid to the fact that the legislation specifying the criteria the fulfilment of which allows for designating a medicine as an orphan medicine, contains a significant number of notions which are not explicitly defined but still do not influence the clarity of the provisions. The Commission Regulation (EC) 847/2000 of 27 April 2000 laying down the provisions for the implementation of the criteria for the designation of a medicinal product as an orphan medicinal product and definitions of the concepts “similar medicinal product” and “clinical superiority”, indicate which documents are to be submitted by the sponsor applying for the designation of a medicine as an orphan medicinal product; however, the issue of how big the sufficient generated return to justify the necessary investment incurred by the pharmaceutical company should be, remains doubtful (OJ L 103, p. 5–8, Art. 2(2)).

The most important role in granting the status of an orphan medicinal product is played by the Committee for Orphan Medicinal Products (hereinafter referred to as “the Committee”) set up within the European Medicines Agency, referred to in Article 4 of Regulation (EC) No. 141/2000.

The main task of the Committee is to examine any application for the designation of a medicinal product as an orphan medicinal product, which is submitted to it by a sponsor. Apart from that, the Committee also advises the Commission on the establishment and development of a policy on orphan medicinal products for the European Union and assists the Commission in liaising internationally on matters relating to orphan medicinal products, and in liaising with patient support groups. The Committee also assists the Commission in drawing up detailed guidelines.

At any stage of the development process of a medicinal product (yet before an application for marketing authorization is filled), the sponsor submits to the Agency an application to obtain a designation for an ‘orphan medicinal product’. The following detailed data and documents are enclosed to the application: a) name and surname or business name and permanent address of the sponsor, b) active substances of the medicinal product, c) proposed therapeutic indication, and d) justification that the criteria laid down in Article 3(1) are met, along with a description of the developmental stages, including the expected indication.

When preparing its opinion, the Committee uses its best endeavors to reach a consensus. If such consensus cannot be reached, the opinion will be adopted by a majority of two-thirds of votes of the

Committee members within 90 days. If the opinion of the Committee is negative, the Agency shall forthwith inform the sponsor as he has 90 days following the receipt of the opinion to submit detailed grounds for appeal, which the Agency shall then submit to the Committee. The Committee will consider at a subsequent meeting whether its opinion might be revised. The Committee meets monthly, which prevents excessive waiting of the sponsor in the case of an appeal against the initial opinion. The Agency immediately forwards the final opinion of the Committee to the Commission, which adopts the decision within 30 days from the receipt of the opinion.

The decision of entering a medicinal product into the EU Register of orphan medicinal products is made by the European Commission. Each year, the sponsor must submit to the Agency a report on the state of development of the designated medicinal product.

To sum up this subject, it should be strongly emphasised that the very designation of a medicinal product as an "orphan" medicinal product does not determine yet whether the marketing authorization can be obtained or not.

The central procedure and reduction of administrative costs

The basic incentive for the development of orphan drugs is the opening of a central procedure regarding the granting of the marketing authorization for medicinal products considered as "orphan" products, even if they do not fulfil the requirements of Regulation (EC) No. 726/2004. The centralized procedure is optional for orphan medicinal products, which means that the method of marketing a medical product depends on the decisions of a pharmaceutical entrepreneur.

Whereas the essence of the concept of a marketing authorization issued by the European Commission is the validity of such marketing authorization throughout the entire European Union, it should be regarded that for entrepreneurs this means conducting one single procedure, the successful completion of which authorizes them to market the medicinal product in each Member State without the necessity of engaging in particular national procedures and conducting 27 separate administrative procedures (5). A central authorization is regarded as the one that grants in each Member State the same rights and imposes the same obligations as any marketing authorization issued by the authorities of a Member State in a decentralized procedure (Art. 12(2) in connection with Art. 13(1) of Regulation (EC) No. 726/2004).

What is important from the perspective of costs related to the centralized procedure, the European Medicines Agency, which gives its opinion on the *dossier* of the orphan drug in this procedure, decreased the costs of the procedure for granting a marketing authorization for orphan medicinal products: the fees regarding the advice for applicants decreased by 80% and other fees by 50%. Apart from that, the Agency annually determines the amount of direct subsidies for usually small companies dealing with the marketing of medicinal products used for the treatment of rare diseases.

The support for industrial property rights

In order to compensate high expenditures incurred by the pharmaceutical industry on the development of orphan medicinal products, the protection rights for these products have been extended.

The sponsor of a medicinal product entered into the EU Register of orphan medicinal products and authorized for marketing in the entire European Union (or based on the authorization issued according to Regulation (EEC) No. 2309/93 or when all Member States issued marketing authorizations in accordance with the procedures of mutual recognition, Art. 19 of the Act of 6 September 2001 on the pharmaceutical law (Journal of Laws 04, No. 53, item 533), according to Article 8 of Regulation No. 141/2000, is granted a 10-year period of market exclusivity for the product. During this period, the relevant authorities are obliged "not to accept another application for a marketing authorization, or issue an authorization, or accept an application to extend an existing marketing authorization, for the same therapeutic indication, in respect of a similar medicinal product". "Similarity" in this case is defined as a similar molecular structure, identical mechanism of action and an equivalent scope of use (6).

Protection granted together with the status of an orphan medicinal product goes much further than the protection resulting from the exclusivity of data, to which the manufacturer of the original medicinal product is entitled according to Article 10 of Directive 2001/83/EC of the pharmaceutical law (7). Referring only to the exclusivity of data, one cannot avoid a situation where another competitive pharmaceutical entrepreneur starts and carries out his own clinical trials and puts on a market a medicine of composition identical to the existing orphan medicinal product. The protection resulting from the status of an orphan medicinal product refers not to the documentation but to specific

substances, and thus makes it impossible to market similar or identical medicines within 10 years.

Apart from that, the relevant authorities issuing a marketing authorization (the Commission or national authorities in case of the procedure of mutual recognition of authorizations), within the period of market exclusivity, cannot allow similar products to be placed on the market, nor can they accept applications in this respect. This is an important provision as the previous practice was that in the period of the 10-year exclusivity the authorities accepted applications and developed them in such a way that directly after the expiry of the exclusivity period, they granted marketing authorizations for similar medicinal products. It means that the effective period of market exclusivity protection related to the status of an orphan drug is thus prolonged by the time necessary for the analysis of applications by the marketing authorities.

However, market exclusivity can be restricted or excluded before the completion of the 10-year period. This applies to cases described in Article 8(2) of Regulation (EC) No. 141/2000. If, at the end of the fifth year of marketing authorization, the criteria laid down in Article 3 are no longer met, the status of an orphan medicinal product may be suspended, effective from the end of the sixth year following the marketing authorization. This applies, for example, to cases where the investor, by marketing the medicine, achieved an economic success; then his market exclusivity is reduced to six years from the date of the marketing authorization.

Apart from the above-mentioned possibility of restricting market exclusivity, Article 8(3) of Regulation (EC) No. 141/2000 provides that authorities regulating the marketing authorization of medicinal products may issue a marketing authorization for a similar orphan drug if the holder of the marketing authorization for the original orphan medicinal product has given a relevant consent to the second applicant, or if the holder of the marketing authorization for the original medicinal product is unable to supply sufficient quantities of the medicinal product, or the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior to the first one.

The provisions of Regulation (EC) No. 141/2000 do not exclude situations where competing investors obtain at the same time the designation of an orphan medicinal product for the

products that they manufacture (an example may be the fact that an agent called arsentrioxid was registered as an orphan medicinal product by three different companies, cf. <http://pharmacos.eudra.org/F2/register/alforphreg.htm>), which *prima facie* may cause a problem with respect to the determination of priority to obtain market exclusivity rights. However, it does not cause any conflicts as the status of an orphan drug and related facilities for the investor are in a sense “launched” after the entrepreneur obtains the marketing authorization. The Regulation thus clearly accepts the rule of “all or nothing” and applies the motto *prior tempore, potior iure*. This means that the first investor who obtained a marketing authorization for his medicinal product may fully use the previously obtained orphan drug status, thus restricting the aspirations of other entrepreneurs, who did not obtain the marketing authorization, for the coming 10 years. It should be emphasized however, that the investor will not benefit if he obtains as the first the marketing authorization for an orphan drug in one Member States only. Only after obtaining the marketing authorization in all EU Member States, may he fully use the instrument of market exclusivity.

Designation of a product as an orphan medicinal product assures special protection, in addition to the patent protection (8), additional protection law (9) and data exclusivity (10).

The specific case of medicinal products used in pediatrics

It is worth noting that approximately 11% of all *orphan drugs*, the status of which is governed by Regulation (EC) No. 141/2000 are intended solely for use in pediatrics (11). Medicinal products used in pediatrics are products authorized for marketing and intended for pediatric use on the basis of clinical trials involving children and adolescents (12). At the EU level, legal aspects of pediatric medicinal products were regulated by Regulation (EC) No. 1901/2006 of 12 December 2006 on medicinal products for pediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC, and Regulation (EC) 726/2004 (OJ L 378, 27. 12. 2006, p. 1).

Regulation (EC) No. 1901/2006 extends the period of market exclusivity for orphan medicinal products from 10 to 12 years, if all the stages of clinical trials were performed according to the approved schedule of clinical trials involving a pediatric group (Art. 37 of Regulation (EC) 1901/2006). In the case of *orphan drugs*, the EU

legislation resigned from the option of extending the protection law by six months to prevent the doubling of incentives. It is worth noting that the bonus of 12-year market exclusivity is also used in the situation where trials conducted on a pediatric group will not allow for authorization with pediatric indication. In such a case however, the results of these trials should be included in the information documents of the medicinal product, in particular in the leaflet enclosed to the packaging (13).

The support of research works

The *ratio legis* of the legal shaping of the status of an orphan medicinal product presented above was supported by the European Union and its Member States through trials, the development of and making orphan medicinal products available, in particular, the support of research works conducted in small and medium-sized enterprises, provided for in the framework programmes for technological research and development. Due to the fact that the development of new possibilities of diagnosing and treating rare diseases as well as carrying out of epidemiological tests in this respect requires action covering many countries in order to increase the number of patients undergoing particular trials, rare diseases remain one of the priorities within the Seventh Framework Programme for research and development (14).

CONCLUSIONS

A response to the question of whether EU regulations will contribute to the development and increased availability of orphan medicinal products is related to the readiness of Member States to undertake actions which in practice will allow for meeting the requirements as set out in Regulation (EC) No. 141/2000, on the basis of the principle of loyal cooperation (Art. 4(3) of the Treaty on European Union as amended by the Treaty of Lisbon). Relevant authorities of Member States are responsible for educating doctors specializing in conducting clinical trials that would confirm therapeutic efficacy of medicines used in rare diseases. A particularly important challenge for Member States is the postulated collaboration with respect to the exchange between centres of specialist knowledge, necessary for the determination of an efficient strategy of dealing with rare disease in Europe. In this context, the Council recommends that Member States should work out and approve, as quickly as possible but preferably no later than until the end of 2013, a plan or a strategy aimed at

directing and conducting appropriate actions with regard to rare diseases within the States' health care and social systems, and indicate appropriate specialist centres in their entire territories until the end of 2013, as well as consider their support for the creation of such centres (point 1a) and point 11 of Council Recommendation of 8 June 2009 on an action in the field of rare diseases).

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