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Access to information supporting availability of medicines for patients suffering from rare diseases looking for possible treatments: the EuOrphan Service[†]

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Summary. Currently in Europe, approximately 30 million people suffer from rare diseases, and a major problem is that many patients do not have access to quality healthcare for their disorders. Moreover, there is also a lack of quality information and a networking system aimed at supporting interaction among patients, clinicians, researchers, pharmaceutical industries, and governmental bodies.

The purpose of this article is to inform physicians, public health care professionals, and other health care providers about EuOrphan service, the aim of which is to ensure easier access to quality information on rare diseases and their treatment. A set of web-based services is available at www.euorphan.com where information for target-users on treatments and products available worldwide for rare disease care as well as indications about healthcare centers are provided. Moreover, the service aims at providing consultancies for pharmaceutical companies to ultimately support the European legislation in bringing new drugs of a high ethical standard to the market and to exert a positive impact on the large population of patients suffering from rare diseases in Europe.

The services provided by EuOrphan can facilitate concrete networking among patients, patient associations, doctors, and companies and also support the organization of clinical trials. In this perspective, EuOrphan could become a very valuable tool for globalizing the information about the availability of treatment (authorized or under development) of orphan patients.

Introduction

Alongside common and more well-known diseases, some 5000–8000 rare diseases (RDs) or disorders have been currently identified. Although affecting relatively few individuals compared to common

diseases, in total they affect the lives of some 30 million Europeans and 25 million North Americans. Each week, five new pathologies are described worldwide, 80% of which have a genetic origin (1–3). The pharmaceutical industry is reluctant to develop medicinal products to treat such diseases (4), as the high costs involved will not be easily recovered. Thus, such products have come to be known as *orphan drugs* (ODs), such diseases *orphan diseases*, and the patient, a *health orphan* (5). This orphan syndrome is made even more acute by the lack of quality information available.

Patients as well as their relatives can feel particularly isolated and vulnerable due to the disease rarity and sometimes even due to their physician's lack of knowledge about their condition and available treatment (4); in fact, the rarer the disease, the scarcer the

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quality information about it. Furthermore, in developed societies, it is unjustifiable that certain categories of patients can be excluded from the benefits of scientific progress and research based on the pretext that the illness from which they suffer is rare (6). Societies all over the world face the challenge, with its countless scientific, medical, economic, and political aspects (7), of bringing efficacious, safe, and affordable medicines to patients in need. Patients suffering from rare disorders should be entitled to effective and appropriate treatment, whether they live in the United States or in the EU (4). The concept of equal access is included in the EU Regulation on orphan drugs, reaffirming that actions at Community level are preferable to uncoordinated measures by Member States (8). In the course of the last decade or so, a number of EU Member States have already adopted specific measures to improve knowledge and care related to RDs (9).

Access to information about a disease is an important and fundamental right, regardless of how common or rare the disease may be. Despite the measures developed to-date, many difficulties still do exist for many people in accessing approved, comprehensive, and high-quality information on RDs and their treatments. Since the US Orphan Drug Act (ODA) was signed in 1983 (10), its success has received widespread attention and has triggered several important international initiatives. In 1991, Singapore established import duty exemption for products used to treat RDs, in 1993, Japan passed an orphan drug law, and in 1997, Australian officials established an orphan drug program based on the ODA (11).

Since 1993, RDs have been a research priority also for the European Commission, when it started its internal discussions on creating necessary incentives to provide patients suffering from RDs with medicinal products which are safe, effective, and produced according to the same quality standards as other medicinal products (12). More than a decade RDs are subject in Community Actions in the field of Public Health. Specific attention has been given to funding the research on RDs in three consecutive EU Framework programs (1).

The EuOrphan project, in which five European countries and 13 research institutions participated, was supported by the European Community, DG Information Society, eTEN program with the aim of contributing to the increase of information about RDs and ODs. Commencing January 1, 2005, the project ended in June 2006. During the 18-month period, a set of web-based services for the dissemination of informa-

tion on the ODs available worldwide has been validated, and from November 2006, the full service is available at www.euorphan.com.

Orphan disease and orphan medicines in the light of legislation

US legislation. The scarcity of products to treat RDs, a worldwide problem, improved somewhat in 1983, when the US Congress passed the Orphan Drug Act (ODA). ODA defined a rare disease or disorder as one that affects less than 200 000 persons in the United States, or as one that even if affecting more than 200 000 persons, no reasonable expectation exists that costs of developing and distributing drugs will be covered solely from their sales (13). The ODA created other financial incentives for drug and biological product manufacturers to stimulate clinical research including tax credits, government grant funding assistance, and a 7-year period of exclusive marketing rights for the first sponsor of an orphan-designated product who obtains market approval from the FDA (14). It has been deemed one of the most successful pieces of health-related legislation in US history thus far (15). At the same time, FDA and National Institutes of Health (NIH) federal programs began to encourage product development as well as clinical research for products targeting rare diseases. In addition, the Rare Diseases Act and Rare Disease Orphan Product Development Act were signed into law in 2002. These acts established an Office of Rare Diseases within the NIH and authorized appropriations for Rare Disease Regional Centers of Excellence (16). Prior to the passage of ODA, approximately 10 drugs met the old definition of orphan drug and had been approved by the FDA (17). Since the implementation of ODA, 1697 medicinal preparations have been designated as orphan products, and with the number of approvals having risen substantially, approximately 10 drugs per year have been approved over the last 23 years (17, 18). As a result, more treatments are available to people affected by rare diseases who once had no hope for survival or improvement of their condition. ODA has resulted in the development of nearly 302 orphan drugs, which are now available on the market for a potential patient population of more than 12 million Americans (19, 20). This was the result of intense lobbying by members of RD communities, including patients, their families, and physicians (17).

EU legislation. A European policy on rare disorders was effectively put into action with the Regulation (EC) 141/2000 adopted on December 16, 1999, setting out a community procedure for the designation of me-

dicinal products and providing incentives for research, development and marketing of orphan medicinal products in the EU (21) on the basis of US experience.

The European Commission's Regulation (EC) No 847/2000 adopted on April 27, 2000, (21) lays down the provisions for the implementation of criteria for designating products as orphan medicinal and defining the concepts of similar medicinal products and their clinical superiority in the context of market exclusivity (22). The European Medicines Agency (EMA) plays a major role in implementing orphan drug legislation, identifying those products eligible for incentives through a Community procedure for orphan designation and providing protocol assistance for orphan medicinal products (22). This means that companies may submit applications for designation as Orphan Medicinal Products to the Committee for Orphan Medicinal Products (COMP) set at the EMA. The criteria for designation (Art. 3) require that the medicinal product would be intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating, or serious and chronic disease that affects less than 5 per 10 000 persons in the Community at the time the application is made, and that no comparably satisfactory method of diagnosis, prevention, or treatment exists (21). If, however, other methods do exist, the medicinal product has to be of significantly higher benefit. A medicinal product can also be designated as an orphan medicine if it is possible to ascertain that without any incentive it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment (21). The lucrative incentive of 10-year marketing exclusivity rights throughout Europe (Art. 8), beginning on the date of the marketing approval may be reduced to six years (at the end of the fifth year of market exclusivity), if the conditions laid down in Art. 8 (1) are no longer met or if the prices charged for the product allow unreasonable profits (13, 21).

The benefits of Regulation (EC) 141/2000 include incentives designed to encourage researchers and pharmaceutical companies to develop and bring forward products for approval as orphan drugs. A major principle outlined by this legislation is also the notion that people affected by diseases treatable by orphan drugs must have the right to receive such treatment: patients with such conditions deserve the same quality, safety, and efficacy in medicinal products as other patients (21). This regulation couples the profit motive of interest of the pharmaceutical industry to the needs of the orphan patient. This supports important notions

such as social justice and equality in society as a whole: individuals with rare disorders share the same desire and rights for effective treatments, which will relieve or remove their conditions, as those with common disorders (24).

The orphan drug legislation is the result of an unwritten commitment between society (or at least governments representing the will of society) and the pharmaceutical industry to undertake research and development programs "without return on investment" in exchange for financial supports and a period of market exclusivity (24). Subsequent legislative changes in the EU Member States show that national health systems are expected to respond to these challenges (21).

Between April 2000 and January 2007, 652 applications for orphan designation were submitted to the EMA with about 400 of them approved. Twenty-nine of these products have gone on to receive marketing authorization through the centralized procedure (25).

The EuOrphan service

Mission. EuOrphan's mission is to disseminate information on rare diseases and orphan medicines available for their treatment in Europe, stimulate the development of new treatments, and facilitate patient accessibility through the dissemination of information on worldwide designated and commercialized orphan drugs. Among its objectives, the service aims at a high positive ethical impact in this underdeveloped and critical health care field. EuOrphan is expected to achieve its mission through the implementation and validation of a set of web-based services accessible at an easy-to-use web portal (www.euorphan.com), based on an up-to-date and reliable IT infrastructure.

EuOrphan services and users. Main user groups of this system are intended to be, most importantly but not only, patients and patient associations, physicians, but also the pharmaceutical industry, public healthcare institutions, researchers, academics, and other health care providers. EuOrphan provides four main types of services, matching the potential user categories:

- An international *database* containing homogeneous and up-to-date information about orphan medicines (both designated and marketed worldwide), including their prices and availability throughout Europe. This service is mainly devoted to *patients, patient associations, physicians (both general practitioners and clinicians)*, who will also have access to educational material and newsletters;

- *Data and statistics* on the orphan market at a world-wide level that will support *public health authorities* and *institutions* in planning rational usage of resources and public health interventions;
- A *consultancy* service by a team of experts that will support *pharmaceutical companies* in defining the business plans for the development of orphan medicinal products (e.g. market statistics, uncovered market sectors) and information for ensuring compliance with regulatory requirements (e.g. epidemiological figures for diseases, support in applying for a designation, etc).
- A *forum* that constitute a means to facilitate the recruitment of patients for clinical trials (of small and geographically dispersed numbers of people) and to organize interest groups and stimulate new studies.

EuOrphan is expected to address and reach a great number of users providing social and ethical benefits to disadvantaged minorities and stimulate pharmaceutical companies to develop and market orphan medicines thus supporting European Legislation, its spirit and vision.

Discussion

A fundamental goal underlying health care and patient's rights is that all people should have access to a high standard of health care (26, 27). Patients have right not only to quality, timely, and appropriate medical care, but also to access high-quality information about the main characteristics, causes, treatments, and prognoses of their disease. Unfortunately, RDs are "invisible" to society and often unknown to health professionals. Moreover, unfamiliarity with standards of care for rare disorders and diseases, both by doctors and patients, often hampers initiatives, while the inherent high-cost/low-demand ratio related to developing quality products to treat these disorders provides little stimulus for the necessary costly research. This poses a real dilemma affecting many lives in Europe and worldwide and is a challenge that can be jointly overcome by health care providers and the people involved in research, development, and politics.

In recent times, medical research and practice have made remarkable progress in diagnosing, treating, and even eradicating a number of diseases worldwide. In addition, in the rare disease field knowledge has been improved in the last years, even if lack of information still exists. On the other hand, RDs require a multidisciplinary approach for their overall management (pharmacological, nutritional, rehabilitation, specific educational strategies, and social support). In such context, the availability of information on both dis-

eases and treatments becomes crucial to support all the involved stakeholders, mainly researches, physicians but also patients and their associations, in managing the diseases and in accessing treatments. The services provided through EuOrphan and freely accessible to all interested parties contribute to disseminate information on orphan drugs in the worldwide perspective.

Even more, the orphan market has a high ethical and social relevance since rare diseases are often serious or life-threatening, few treatments are usually available, and despite the rarity, they affect a large number of people. Consequently, there is also a strong interest both from public institutions, with a responsibility of meeting the demand and authorizing safe and effective drugs, and from industries aimed at increasing their competitiveness by developing niche innovative drugs. EuOrphan objective is also addressed to meet the needs of pharmaceutical companies and governments. It seeks to promote the EU Regulation on orphan drugs by stimulating the development of new drugs in Europe and promoting European public health and research policies on rare diseases.

The process of inventing a new medicine and bringing it to the market is generally complex, long, and expensive. Within this process, the clinical development plays a key role that in cases of RDs, often encounters many difficulties. At the EU regulatory level, some initiatives have been undertaken; among these guidelines on clinical trials in small populations were recently released by the EMEA, which outline provisions to be followed in the research and development of orphan medicinal products (22, 28). The conduction of multicenter clinical trials (CTs) could also enhance the knowledge on safety and efficacy of orphan products not only for their use in Europe, but also worldwide. This knowledge together with information on CTs in progress in the EU could promote the use of safe and efficient drugs in EU countries. For example, in the Baltic countries of Estonia, Latvia, and Lithuania, significant numbers of CTs are approved each year, showing that in these countries Competent authorities are gaining significant experience in the area. However, even after implementation of the EU Directives in national legislation, the number of CTs aimed at investigating orphan medicinal products remains low.

Conclusion

The services provided by EuOrphan can facilitate concrete networking among patients, patient associa-

tions, doctors and companies and also support the organization of clinical trials, sharing experts and possibly favoring the recruitment of patients, a crucial aspect in designing clinical trials for rare diseases. In

this perspective, EuOrphan could become a very valuable tool for globalizing the information about the availability of treatment (authorized or under development) of orphan patients.

EuOrphan paslauga – informacija apie vaistų, skirtų gydyti sergančiuosius retomis ligomis, prieinamumą

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Raktažodžiai: retos ligos, retieji vaistai, retomis ligomis sergantys pacientai, informacija, įstatymai.

Santrauka. Europoje retomis ligomis serga maždaug 30 milijonų žmonių. Viena pagrindinių problemų – ribotos tokių pacientų galimybės gauti atitinkamos kokybės sveikatos priežiūros paslaugas, išsamios informacijos stoka, taip pat duomenų bazių, didinančių pacientų, gydytojų, mokslininkų, farmacijos pramonės bei valdžios atstovų bendradarbiavimo galimybes.

Straipsnio tikslas – informuoti įvairių specialybių gydytojus, visuomenės sveikatos ir kitus sveikatos priežiūros specialistus apie *EuOrphan* paslaugą, kurios uždavinys – palengvinti informacijos apie retas ligas ir jų gydymą prieinamumą. Šia paslauga galima pasinaudoti interneto duomenų bazėje adresu: www.euorphan.com, kur vartotojams teikiama informacija apie retų ligų gydymą, pasaulinėje rinkoje esančius retųjų vaistų kategorijai priskirtus vaistinius preparatus, sveikatos priežiūros įstaigų teikiamas paslaugas retomis ligomis sergantiems pacientams, farmacijos įmonės gali gauti ekspertų konsultacijas dėl klinikinių tyrimų organizavimo ir šiuo metu vykdomų klinikinių tyrimų, retų ligų paplitimo statistikos, vaistų priskyrimo retiesiems, jų registravimo klausimais.

EuOrphan paslauga – tai galimybė užmegzti ryšius tarp pacientų, sergančių retomis ligomis, pacientų organizacijų, gydytojų bei farmacijos įmonių, taip pat galinti palengvinti ir klinikinių tyrimų organizavimą. *EuOrphan* – vertingas informacijos šaltinis retomis ligomis sergantiems pacientams apie visoje Europos Sąjungoje ir už jos ribų esančius vaistus (jau registruotus ar dar kuriamus) retų ligų diagnozavimui, profilaktikai arba gydymui.

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References

1. Van Weely S, Leufkens HGH. Orphan diseases. In: Kaplan W, Laing R, editors. Priority medicines for Europe and the world – a public health approach to innovation. Geneva: World Health Organization; 2004. p. 95-100.
2. Tambuyzer E. The European orphan medicinal products regulation and biotechnology-based industry in Europe. J Commerce Biotechnol 2000;6:340.
3. French national plan on rare diseases 2005–2008. Ensuring equity in the access to diagnosis, treatment and provision of care. 2004 Nov 20 [cited 2007 Mar 28]. Available from: URL: http://www.eurordis.org/IMG/pdf/EN_french_rare_disease_plan.pdf
4. Cooke E. The European regulation on orphan medicinal products. Pharmaceutical Policy and Law 2001;3:11-7.
5. Laurence DR, Bennett PN, Brown MJ. Clinical pharmacology. 8th ed. Discovery and development of drugs. Oxford: Churchill Livingstone; 1997. p. 40-6.
6. Grossette F. Research and development of orphan drugs: at least a European regulation. Pharmaceutical Policy and Law 2001;3:7-9.
7. Stolk P, Willemsen M, Leufkens HG. Rare essentials? Drugs for rare diseases on the essential medicines list. A discussion paper prepared for the WHO Expert Committee on the Selection and Use of Essential Medicines. Bull World Health Organ 2006;84(9):745-51.
8. Rappagliosi A. Patient access to innovation: biopharmaceuticals, 4th hurdles and socioeconomic issues. J Commerce Biotechnol 2001;4:299-308.
9. Fischer A, Borensztein P, Roussel C. The European rare diseases therapeutic initiative. A public-private partnership is promoting research on new treatments for rare diseases. PLoS Med 2005;2(9):e243.
10. US Food and Drug Administration. The Orphan Drug Act. 1983 [cited 2007 Feb 20]. Available from: URL: www.fda.gov/orphan/oda.htm
11. Cheung RY, Cohen JC, Illingworth P. Orphan Drug Policies: implications for United States, Canada and developing countries. Health Law J 2004;12:190.
12. Inventory of Community and Member States incentive meas-

- ures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005. Available from: URL: http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/doc/inventory_2006_08.pdf
13. De Luca G. Orphan drugs and patents: an attempt to clarify the relationship existing between these two systems. *Pharmaceutical Policy and Law* 2001;3:63-9.
 14. Haffner ME, Whitley J, Moses M. Two decades of orphan product development. *Nat Rev Drug Discov* 2002;1:821-5.
 15. Casteels B, Rappagliosi A. Rare diseases and medical devices in the European Union. *Pharmaceutical Policy and Law* 2001; 3:69-78.
 16. Iribarne A. Orphan diseases and adoptive initiatives. *JAMA* 2003;290:116.
 17. Thoene JG. Orphan drugs and orphan tests in the USA. *Community Genet* 2004;7(4):169-72.
 18. Cumulative list of all orphan designated products; effective: 2/26/2007 [cited 2007 Mar 1]. Available from: URL: <http://www.fda.gov/orphan/designat/alldes.rtf>
 19. Rados C. Orphan products: hope for people with rare diseases. *FDA Consum* 2003;37(6):10-5.
 20. Cumulative list of all orphan designated products approved for marketing. Effective: 2/26/2007 [cited 2007 Mar 1]. Available from: URL: <http://www.fda.gov/orphan/designat/allap.rtf>
 21. Regulation (EC) No 141/2000 of the European Parliament of the Council of December 16, 1999 on Orphan medicinal products. OJ L 18/1-5, 22.1.2000.
 22. Le Courtois P, Carr M. Orphan medicinal products – the role of the EMEA. *Pharmaceutical Policy and Law* 2001; 3:31-5.
 23. Commission Regulation (EC), No 847/2000 of 27 April 2000, OJ L103/5, 28.4.2000.
 24. Rappagliosi A. Patient access to orphan drugs in the European Union. *Pharmaceutical Policy and Law* 2001;3:55-61.
 25. The Community Register of orphan medicinal products for human use. Available from: URL: <http://ec.europa.eu/enterprise/pharmaceuticals/register/index.htm>
 26. The Community Register of orphan medicinal products for human use. Available from: URL: <http://ec.europa.eu/enterprise/pharmaceuticals/register/index.htm>
 27. WHO Regional Office for Europe, Declaration on the Promotion of Patients' Rights in Europe, reprinted in 45 International Digest of Health Legislation 411 (1995 Available from: URL: <http://www1.umn.edu/humanrts/instree/patientrights.html>
 28. Guideline on clinical trials in small populations. London, 27 July 2006, CHMP/EWP/83561/2005. Available from: URL: <http://www.emea.eu.int/pdfs/human/ewp/8356105en.pdf>

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