BIO DEUTSCHLAND

Background Paper by BIO Deutschland

on

the Legislative Framework for Orphan Medicinal Products

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Introduction

"Patients with rare diseases are the orphans of the healthcare system. Their disease often remains undiagnosed and there are no therapy options or research. This means that they have no grounds for hope."

Eurordis (2005). European Conference on Rare Diseases. Luxembourg 2005

The Biotechnology Industry Organisation (BIO Deutschland), the trade association of the German biotechnology sector, aims to provide information in this background paper on the legal status and ramifications of European and German regulations on medicinal products for rare diseases (also known as orphan medicinal products or orphan drugs).

The field of orphan medicinal products involves particular challenges for doctors and pharmaceutical manufacturers. Rare diseases form a highly heterogeneous group of mainly complex symptoms, which are genetic in 80 per cent of the cases and mostly severe and chronic. Patients with rare diseases need comprehensive and specialised care. In adopting Regulation (EC) No 141/2000 (abbreviated as 141/2000/EC) on orphan medicinal products, the EU aimed to specifically promote research and development on such drugs. Over four million people in Germany suffer from a rare disease.[1] A disease is defined as rare if it affects not more than five in 10,000 persons. These diseases are usually chronic, progressive, degenerative and often life-threatening. As a result, they are often of a highly impairing nature and have a severe impact on the quality of life of patients and those close to them. Small and medium-sized biotechnology enterprises in particular are highly active in the field of rare diseases.

Of the some 30,000 known diseases, up to 8,000 are classified as rare. Thanks to the significant increase in drug developments for these symptoms, there is hope for the some four million people affected by a rare disease in Germany and for their relatives. This means that the above quotation fortunately no longer applies to all patients with a rare disease. Since the introduction of orphan-drug status under Regulation 141/2000/EC, 58 orphan medicinal products have been granted marketing authorisation. German biotechnology companies are enjoying similar successful results with further niche medicines that do not come under Regulation 141/2000/EC, but are also produced for a small market and have a very low impact on the drug budget. This research by biotechnology companies is of immense importance, as it provides new hope that therapy options will finally become available for an increasing number of rare diseases. Now we must ensure that the progress that has resulted from the introduction of orphan-drug status and state funding is not negated by greater difficulties in reimbursement for orphan medicinal products and the establishment of lower prices. The same applies to the currently planned German and European initiatives on improving the situation of people with rare diseases.[2]

[1] Information by the Alliance for Chronic Rare Diseases (ACHSE) at www.achse-online-de. (Available in German only.)

[2] Please see the suggestions by the European Commission in its Communication on Rare Diseases: Europe's Challenges, COM (2008) 679; the Council's recommendation on an action in the field of rare diseases (2009/C 151/02); and Eidt et al. "Maßnahmen zur Verbesserung der gesundheitlichen Situation von Menschen mit seltenen Erkrankungen in Deutschland"- Studie im Auftrag des Gesundheitsministeriums, 2009 ["Measures to Improve the Health Situation of People with Rare Diseases in Germany. A Study Commissioned by the German Federal Ministry of Health, 2009"]

The European legislative framework on orphan medicinal products

For many years, hardly any medicinal products were developed for rare diseases, as this was not worthwhile for pharmaceutical companies.[3] In order to provide people suffering from rare diseases with the same access to diagnostics and therapy as people with common diseases, the EU adopted Regulation (EC) No 141/2000 on orphan medicinal products over ten years ago. The regulation's primary purpose was to make it easier for companies to develop orphan medicinal products by providing financial incentives and setting up funded projects. Without targeted support, the chances of recouping the development costs and generating additional revenue to develop the product further and to develop new products are almost non-existent, particularly in the case of small and medium-sized biotechnology enterprises, which are very active in this field. On 9 June 2009, the EU health ministers also adopted a recommendation by the Council of Ministers calling on the member states to develop and implement a plan and strategies on treating rare diseases. As a result, the German Federal Government set up a National Action League for People with Rare Diseases (NAMSE) in March 2010. This organisation is tasked with producing a national action plan for improving the care situation. In addition, a series of funded projects on the European and German level (e.g., the E-Rare project funded by the EU's Framework Programme for research and Go-Bio, which is funded by the Federal Government's High-Tech Strategy for Germany) aim to make it easier to found biotechnology companies and to facilitate research projects by small and medium-sized enterprises. While hardly any orphan medicinal products were launched on the market before 2000, one result of the funding schemes has been the authorisation of 58 orphan medicinal products to date[4]. However, there is still a great need for research. The funding is effective, but the objective is still a long way from being met.

Regulation (EC) No 141/2000 on orphan medicinal products (referred to hereinafter as 141/2000/EC) defines the following aims:

- to provide incentives to the pharmaceutical and biotech industry for the research, development and placing on the market of orphan medicinal products[5];
- to establish a Committee for Orphan Medicinal Products (COMP) within the European Agency for the Evaluation of Medicinal Products. (This organisation was renamed the European Medicines Agency (EMA) in 2005). COMP is responsible for inspecting applications from private individuals or companies that plan to develop orphan medicinal products. It also advises investors and supports the European Commission in all discussions and decision-making processes involving orphan medicinal products.

These aims are met via incentives for research and development on medicinal products for the diagnosis, prevention or treatment of rare diseases. A company developing this type of product must first apply for orphan-drug status. Medicinal products are granted this status under the very tight conditions of Article 3, paragraph 1 of 141/2000/EC. In addition to the indications of a rare disease, the applicant must prove that no satisfactory method for treating the condition has been authorised so far in the EU or that the medicinal product in question will be of significant benefit in comparison with the existing therapy or therapies. Hence, orphan medicinal products must meet three criteria:

- severe illness ("*a life-threatening, seriously debilitating or serious and chronic condition*"[6])
- innovation ("*there exists no satisfactory method*"[7] to date) or additional benefit (will be "*of significant benefit*"[8])
- rarity ("*affecting not more than five in 10 thousand persons*"[9]).

COMP checks whether these criteria are met. It then submits an evaluation report to the European Commission, which in turn decides whether or not to grant orphan-drug status (Article 5 of 141/2000/EC).

[3] Also cf. recital 1 of Regulation (EC) No 141/2000.
[4] Orphanet database (http://www.orpha.net/consor/cgi-bin/Drugs_ListOrphanDrugs.php?lng=EN).
[5] In line with Article 1 of Regulation (EC) No 141/2000.
[6] Cf. Article 3, paragraph 1(a) of Regulation (EC) No 141/2000.
[7] Cf. Article 3, paragraph 1(b) of Regulation (EC) No 141/2000 and Article 2, paragraph 3 of Regulation (EC) No 847/2000.
[8] Cf. Article 3, paragraph 1(a) of Regulation (EC) No 141/2000 and Article 3, paragraph 2 or Regulation (EC) No 847/2000.
[9] Cf. Article 3, paragraph 1(a) of Regulation (EC) 141/2000.

Companies receive the following benefits as incentives:

- They are entitled to free advice from the European authorisation agency on the conduct of the clinical trials necessary for authorisation of an orphan medicinal product (Article 6 of 141/2000/EC).
- The marketing authorisation fees for orphan medicinal products can be waived in part or in total (Article 7, paragraph 2 of 141/2000/EC).[10]
- Data or market exclusivity (Article 8 of 141/2000/EC) for a period of ten years in the EU.

Apart from these points, orphan medicinal products are subject to the normal authorisation criteria applicable to other medicinal products.[11]

The market exclusivity right should not impinge on existing intellectual property rights. Furthermore, it is limited to the therapeutic indication for which orphan medicinal product designation has been granted. *"In the interest of patients, the market exclusivity granted to an orphan medicinal product should not prevent the marketing of a similar medicinal product which could be of significant benefit to those affected by the condition."*[12] Hence, the exclusivity right, which fundamentally applies for a period of ten years, is checked at the end of the fifth year. It expires if another company can prove that its medicinal product is "safer, more effective or otherwise clinically superior" during the ten-year period.[13]

Orphan-drug status is granted for a particular indication. It is not possible to extend this indication at a later stage. This is also laid down in Article 7, paragraph 3 of Regulation (EC) 141/2000: *"The marketing authorisation granted for an orphan medicinal product shall cover only those therapeutic indications which fulfil the criteria set out in Article 3. This is without prejudice to the possibility of applying for a separate marketing authorisation for other indications outside the scope of this Regulation."* If marketing authorisation for a new therapeutic indication is granted, the company is by no means automatically granted orphan-drug status. It must provide proof for this new therapeutic indication.[14] Furthermore, extensions of the therapeutic indication must always be authorised and thus require research activities (particularly the conducting of phase I to III clinical trials).

As the European Commission correctly noted in its communication on rare diseases, *"the EU policy for orphan drugs is a success. However, Member States do not yet ensure full access to each authorised orphan drug approved."*[15]

Berlin, 13 September 2011

[10] Cf. EMA "Fee reductions for designated orphan medicinal products", 15 February 2011. (http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/02/WC500102327.pdf)

[11] This is stated clearly in recital 7 of Regulation (EC) No 141/2000: "Patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients; orphan medicinal products should therefore be submitted to the normal evaluation process". This is also stated by the European Commission: http://europa.eu/legislation_summaries/internal_market/single_market_for_goods/pharmaceutical_and_cosmetic_products/l21167_en.htm

[12] Cf. recital 8 of Regulation (EC) No 141/2000

[13] Article 8, paragraph 3(c) of Regulation (EC) No 141/2000.

[14] Clarified under Article 2, No. 4(a) of Regulation (EC) No 847/2000.

[15] European Commission Communication on Rare Diseases: Europe's Challenges, COM (2008) 679.

Further information on orphan medicinal products

1. Directorate-General for Enterprise and Industry of the European Commission
   - Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products (2005 revision) - http://ec.europa.eu/health/files/orphanmp/doc/inventory_2006_08_en.pdf
   - Final Conclusions and Recommendations of the High Level Pharmaceutical Forum (October 2008) - http://ec.europa.eu/pharmaforum/docs/final_conclusions_en.pdf
2. Directorate-General for Health and Consumers of the European Commission
   - RDTF Report – Overview of Current Centres of Reference on rare diseases in the EU (September 2005) - http://www.eucerd.eu/upload/file/Publication/RDTFECR2005.pdf
   - RDTF Report: Centres of Reference for Rare Diseases in Europe – State-of-the-art in 2006 and recommendations of the Rare Diseases Task Force (September 2006) - http://www.eucerd.eu/upload/file/Publication/RDTFECR2006.pdf
   - RDTF Report – State of the Art and Future Directions (March 2008) - http://www.eucerd.eu/upload/file/Publication/RDTFERN2008.pdf
   - RDTF Report: Health Indicators for Rare Diseases: State of the art and future directions (June 2008) - http://www.eucerd.eu/upload/file/Publication/RDTFHI2008.pdf
   - RDTF Report: How many drugs for how many patients (July 2007) - http://www.eucerd.eu/upload/file/Publication/RDTFOD2007.pdf
   - RDTF Report: Health Indicators For Rare Diseases - Conceptual Framework And Development Of Indicators From Existing Sources (April 2010) - http://www.eucerd.eu/upload/file/RDTFReportIndicatorsApril2010.pdf
   - EUCERD Report: Initiatives and Incentives in the field of rare diseases (July 2010) - http://www.eucerd.eu/upload/file/Reports/2009ReportInitiativesIncentives.pdf
   - EUCERD Report: Preliminary analysis of the outcomes and experiences of pilot European Reference Networks for rare diseases (May 2011) - http://www.eucerd.eu/upload/file/Reports/2011ERNAnalysis.pdf
3. Directorate-General for Research and Innovation of the European Commission
   - International Rare Disease Research Consortium (IRDiRC) First Workshop Summary Report - http://ec.europa.eu/research/health/medical-research/pdf/reykjavik-workshop-report_en.pdf
   - International Rare Disease Research Consortium (IRDiRC) Second Workshop Summary Report - http://ec.europa.eu/research/health/medical-research/pdf/rare-diseases/executive-summary_en.pdf
4. European Medicines Agency (EMA)
   - European Medicines Agency Annual Report for 2008 - http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2009/12/WC500016589.pdf
   - European Medicines Agency Annual Report for 2009 - http://www.ema.europa.eu/docs/en_GB/document_library/Annual_report/2010/05/WC500090712.pdf
   - European Medicines Agency Annual Report for 2009/2010 - http://www.ema.gov.sg/media/files/annual_reports/EMA_Annual_Report_2010.pdf
   - COMP recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation (EMA/COMP/15893/2009) - http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/07/WC500095341.pdf

Selected links on orphan medicinal products:

- Information by the German Federal Ministry of Health on orphan medicinal products (available in German only) - http://www.bmg.bund.de/praevention/gesundheitsgefahren/seltene-erkrankungen.html
- Information by the German Federal Ministry of Education and Research on rare diseases (available in German only) - http://www.gesundheitsforschung-bmbf.de/de/131.php
  An English flyer can be downloaded at http://www.gesundheitsforschung-bmbf.de/_media/SeltErkrank_11.2006_engl.pdf.
- German National Action League for People with Rare Diseases (available in German only) - http://namse.de/. A brief summary in English is available at http://www.namse.de/images/stories/Dokumente/Gemeinsame_Erklrung-13-03-2012-Engl.pdf.
- Orphanet, the portal for rare diseases and orphan drugs - http://www.orpha.net/consor/cgi-bin/index.php?lng=EN
- Alliance for Chronic Rare Diseases - ACHSE e.V. (available in German only) - http://www.achse-online.de/
- ACHSE's information portal (available in German only) - http://achse.info/
- The European Commission's webpage on rare diseases - http://ec.europa.eu/health/rare_diseases/policy/index_en.htm
- Eurordis– the European alliance of patient organisations and individuals active in the field of rare diseases - http://www.eurordis.org/
- European Union Committee of Experts on Rare Diseases (EUCERD) - http://www.eucerd.eu/
- European Project for Rare Diseases National Plans Development (EUROPLAN) - http://www.europlanproject.eu/Home.aspx

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The Biotechnology Industry Organisation Deutschland (BIO Deutschland) has set itself the objective of supporting and promoting the development of an innovative economic sector in Germany based on modern biosciences. The association currently has over 280 members, which include companies, BioRegions and sector service providers. **Dr Peter Heinrich** (CEO of MagForce Nanotechnologies AG) is Chairman of the Board of BIO Deutschland.

BIO Deutschland's supporting members and partner organisations are as follows: **berlinbiotechpark GmbH**, **Celgene GmbH**, **CMS Hasche Sigle**, **Commerzbank AG, Deutsche Bank AG, EBD Group, Ernst & Young AG, KPMG AG, Miltenyi Biotec GmbH, Merck KGaG, MLawGroup, PricewaterhouseCoopers AG, Sanofi-Aventis Deutschland GmbH, SAP Deutschland AG & Co. KG** and **TVM Capital GmbH**.

You are welcome to request further information on the activities of BIO Deutschland and its working groups from the association's office or at www.biodeutschland.org.

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