Article UK JIMS 2010: Rare Diseases & Orphan Drugs, a comprehensive approach of strategic perspectives

Key words: Orphan Diseases, Orphan Drugs, Strategy, Market,

Summary

During the past 30 years Rare Diseases and Orphan Drugs have experienced a growing focus from health authorities and the pharmaceutical industry due to the huge lobbying of patients' associations. Today this segment of the healthcare market enters the maturity stage. This paper proposes an overview from the available literature and experience of stakeholders, with a special focus on key strategies that made this segment a viable and ever growing market. In addition, it highlights the specificities and the common ground regarding Rare Diseases and Orphan Drugs compared to common diseases and classic drugs.

Introduction

Many Health Authorities have progressively developed a dedicated strategy for Rare Diseases over the past 30 years. The 1983 Orphan Drug Act in the USA was followed by the establishment of the Office of Rare Diseases in 1993 and the Rare Diseases Act in 2002[1]. Whilst in Europe, Eurordis was established by a coalition of patient-support groups and the European Union in 1997[2], followed by the Regulation (EC) No 141/2000 on orphan medicinal products and its related Committee for Orphan Medicinal Products (COMP)[3], then by Orphanet, a web-based database of Rare Diseases, centres of excellence and patient-support groups[4]. Furthermore, France has published a national strategy for Rare Diseases, which includes specific training at all stages of medical education in the recognition and treatment of

[1] Office of Legislative Policy and Analysis. Rare Diseases Act. 2002. http://olpa.od.nih.gov/legislation/107/publiclaws/raredisease.asp

[2] Eurordis. European Organisation for Rare Diseases. Rare diseases:understanding this public health priority. 2005. http://www.eurordis.org/IMG/pdf/princeps_document-EN.pdf

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

[4] Orphanet. http://www.orpha.net/consor/cgi-bin/home.php?Lng=GB

Rare Diseases[5]. Outside Europe, New Zealand, Canada as well as Australia, all have an orphan drug program[6].

Country	Public health initiative for Orphan Drugs
Belgium	Groupe Pilotage Maladies rares / Stuurgroep Zeldzame Ziekten
Bulgaria	Information Centre for Rare Diseases and Orphan Drugs - Bulgaria National Plan for Rare Diseases 2009-2013
Denmark	The Danish Centre for Rare Diseases and Disabilities
Finland	Väestöliitto - Network of Reference Centres for Rare Diseases - Harvinaiset Sairaus
France	Plan National Maladies Rares (2005-2008) - List of Centres of Reference for Rare Diseases in France - GIS-Institut des maladies rares - Maladies Rares Info Services - Help line on Rare Diseases
Germany	Rare Diseases, the Networks – Federal Ministry of Education and Research
Hungary	Veleszületett Rendellenességek és ritka betegségek Országos Felügyelete (National Center of Surveillance for Congenital Anomalies and Rare Diseases)
Italy	Centro Nazionale Malattie Rare - Rete Nazionale Malattie Rare
Luxembourg	Groupe de Travail Maladies Rares
Norway	Senter for sjeldne diagnoser (Center for rare diagnoses) - FRAMBU Centre for Rare Disorders
Portugal	Programa Nacional para Doenças Raras / National Plan for Rare Diseases
Spain	Centro de Investigación Biomédica en Red de Enfermedades Raras - National Provincial Atlas of Rare Diseases 1999-2003 (Spain) – 2006 - Instituto Carlos III – Instituto de Investigación de Enfermedades Raras - Enfermedades raras en Extremadura 2004 (epidemiological report prepared by the Regional Government of Extremadura)
Sweden	SmågruppsCentrum - Swedish National Centre for Rare Diseases - Rare Diseases in Sweden
The Netherlands	Dutch Steering Committe on Orphan Drugs
United Kingdom	National Specialist Commissioning Advisory Group – Department of Health - List of centres of reference in UK by type of centre
United States	National Institutes of Health - Office of Rare Diseases

The main focus of those strategies has been to support the coordination of disease-based support groups, dissemination of information about Rare Diseases, and research into commercially non-viable treatments, providing adequate health insurance and coverage of medical expenses. Those strategies appear to have had some success in increasing access to these drugs[7]. However this was achieved because pharmaceutical companies responded to the need and developed their own development strategy to reach a financial balance within the regulatory frame given the commercial imperative to maximise revenue and minimise costs. The pharmaceutical industry acknowledged the strategic opportunity that the licensing legislation for orphan drugs represents as early as 2004[8]. In response, the ability of the

[5] French National Plan for Rare Diseases 2005–2008. Ensuring equity in the access to diagnosis, treatment and provision of care(2004). http://www.eurordis.org/IMG/pdf/EN_french_rare_disease_plan.pdf

[6] Knight AW and Senior TP. The common problem of rare disease in general practice. MJA 2006;185(2):82-83.

[7] Department of Health and Aged Care. The orphan drug program and improving community access to effective drugs for rare diseases. 2001 http://www.tga.gov.au/docs/pdf/orphrev.pdf

[8] De Varax A, Lettelier M, Bortlein M. Study on orphan drugs. Phase II:consideration on the application of article 8.2 of EU regulation 141/2000 concerning orphan drugs. Paris:Alcimed, 2004.

pharmaceutical industry to take a strategic approach to the development process in order to optimise the amount of public financing and minimise the financial risk was highlighted by the National Institute for Health and Clinical Excellence (NICE) in 2005[9]. Public-private partnerships, which are promoted by the legislation regarding Orphan Drugs development, involve joint investment of resources by bodies including universities, government supported research organisations, pharmaceutical companies, venture capitalists and research based charities[10].
Within the Marketing field, Strategy deals with the planning and conduct of the life cycle of a product or a service. It integrates the intrinsic characteristics, both strengths and weaknesses of the product or the service it serves as well as the contextual facts or circumstances (opportunities and threats) surrounding the product or service. Planning is a cognitive process that formulates concepts, fixes objectives and the relevant program for a definite course of action in order to attain the goal, which is believed to be accomplishable. Conduct is the way to manage/control/direct the course of the relevant program dedicated to advocate the product or service to the target audience.
This scheme has been elaborated by "big pharma" companies dealing with so-called "blockbusters" that treat common diseases affecting large populations of patients. Indeed, the correct strategy differs for diseases, drugs, patient populations and competitive pressure.
There is no question that, in order to develop and survive, pharmaceutical companies involved in the field of Rare Diseases and Orphan Drugs are compelled to follow their lead.
But what kind of strategy applies? In other words, what are the specificities and the common ground regarding Rare Diseases and Orphan Drugs compared to common diseases and classic drugs?

Materials and Methods

In order to propose a comprehensive approach of strategic perspectives regarding Rare Diseases & Orphan Drugs, the following sub questions have been addressed:

- To propose a definition of Rare Diseases
- To picture the epidemiology of Rare Diseases
- To analyse the regulatory status of Orphan Drugs
- To evaluate Clinically Orphan Drugs appraisal
- To overview the Orphan Drugs Market
- To identify potential limitations of Orphan Drugs
- To identify Key Success Factors for approval
- To propose Key Success Factors for market development

A literature review of relevant publications identified in the Medline database as well as on certain websites dedicated to Rare Diseases and Orphan Drugs was therefore used as the basis for this publication. This work was completed by interviews with stakeholders of the Rare Diseases and Orphan Drugs.
"Rare Diseases" exists as a MeSH Term of the Medline database and is related to 2706 articles (August 2010). Because "Rare Diseases" are linked with the concept of community commitment, the first filter was the ability to have access to the full free text, which narrowed the selection down to 339 articles.

[9] McCabe C, Claxton K, Tsuchiya A. Orphan drugs and the NHS should we value rarity? BMJ. 2005;331(7523):1016-9.
[10] Rawlins MD. Neglected diseases "Priority medicines for Europe and the world" is a wake up call from WHO. BMJ. 2005;330(7488):376-7.

Then it appeared that the Medline MeSH term “Rare Disease” does not discriminate between Rare Diseases, Neglected Diseases and to some extent Rare Cancers. Although both first diseases share the same public health challenge, they are different and should be discriminated against[11]. “Rare Cancers” tend to overlap with “Rare Diseases” and patients sometimes can get confused. France is the first country in which, since 2009, patients can be referred to certified centres of excellence dedicated to “Rare Cancers”[12]. “Neglected Diseases” and “Rare Cancers” were therefore considered as exclusion criteria. Since the objective is not to explore every single Rare Disease but rather the overall concept, articles focusing on a single condition, case studies and clinical trials were excluded. Along this selection process 62 articles relevant to the topic as well as being published between 2005 and 2010 were selected (see more details in Chart A in the Appendix).

Surprisingly, regarding MeSH Terms, Orphan Drug has only one main entry, “orphan drug production” with 525 related articles (August 2010) but not “orphan drug” alone. Because this doesn’t cover our topic, it has not been used. Because of this limitation of the MeSH Terms system, the search strategy ("orphan drug"[Title/Abstract]) AND "marketing"[MeSH Terms] have been used. It retrieved 8 publications without any timeline restriction (see more details in Chart B in the Appendix).

Although a key criterion for Orphan Drug endorsement by European Health Authorities, "significant benefit" is not a MeSH Term in the Medline database. The search strategy ("significant benefit"[Title/Abstract]) AND "orphan drug"[Title/Abstract] retrieved only 2 articles (August 2010). One is dedicated to Drug Therapies for Cognitive Impairment and Dementia and therefore has been excluded according to our exclusion criteria and the other one is in Chart C in the Appendix).

Additional searches where conducted to respond to specific needs and are therefore referenced in the body of this article. Some of the additional searches of Rare Diseases dedicated websites content as well as those of patient associations and pharmaceutical industries (see complete list in Chart D, E & F in the Appendix).

Results

Overview of searched literature

The difficulty in finding relevant literature on Rare Diseases and Orphan Drugs was pointed out as early as 2006[13]. Nevertheless sufficient material has been collected to respond to initial questions. Regarding publications related to Rare Diseases different periods of time are identified.
From 2005 until early 2006, articles are mainly elicited by the NHS and the NICE and point out the financial issues arising from the Orphan Drugs market development and its potential impact on Healthcare resources.

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[11] Fehr A, Thürmann P, Razum O. Editorial drug development for neglected diseases a public health challenge . Trop Med Int Health. 2006;11(9):1335-8.
[12] Plan Cancer 2009-2013. Institut National du Cancer 2009. (action 23.1).
[13] Silfen EZ, Patel C, Mendonça E, et al. searching rare medical diagnoses and retrieving relevant citations. AMIA Annu Symp Proc. 2006:1094.

In 2006 articles focus on the management of Rare Diseases' patients. They are elicited by British and Spanish physicians. Discussions on Orphan Drugs focus more on status and differences with "essential medicines" linked with Neglected Diseases.
In 2007 issues regarding biostatistics are discussed along with web oriented solutions to improve quality information and networking systems aimed at supporting interaction among patients, clinicians, researchers, pharmaceutical industries and governmental bodies.
In 2008 Spanish physicians are the major contributors of a comprehensive overview of Rare Diseases calling for multidisciplinary interventions that deal with the negative impact of these diseases on the people affected and their families. Biostatistic models adapted to small numbers are discussed further by British authors.
In 2009-2010 articles address issues regarding recruitment of patients in clinical trials with a special emphasis on Web solutions.

Rare Diseases description

Worldwide, there are an estimated 6000 to 7000 Rare Diseases[14]. The EU's definition of a Rare Disease is when it affects less than 5 persons per 10 000[15]. In fact, "Rare Diseases" is a collective term that includes a very heterogeneous group of complex disorders that can affect any bodily system. Not to confuse with Neglected Diseases, a group of 13 tropical infections affecting the world's poorest people (and a cause of poverty by themselves), who also experience a shortage of safe and effective treatments[16,17].
In some instances, symptoms are apparent at birth or during early childhood, as is the case in several inherited metabolic diseases such as phenylketonuria, Lesch-Nyhan syndrome or Kearns-Sayre syndrome, as well as several neurological disorders such as Rett syndrome, in Osteogenesis Imperfecta and related collagen and bone diseases or Haemophilia. Many Rare Diseases, however, appear only in adults[18]. Most Rare Diseases, which are genetic disorders, are often severely disabling and can impair physical and mental disabilities. These disabilities result in a reduced quality of life, and affect an individuals' learning capacity and as a result they can affect their chance to have an education[19].
Another aspect of Rare Diseases is that they are either visible or non-visible to the general public depending on body parts involved with the disease. Visible Rare Diseases represent 5.9% of ICD-9-CM codes. These diseases include tumours, endocrine disorders, orofacial abnormalities, infectious diseases, gait, posture and stature disorders, disorders of the limbs?, developmental malformations, metabolic disorders, central nervous system abnormalities, peripheral nervous system disorders, and post-traumatic effects[20]. Regardless whether they are visible or not, Rare Diseases also pose a considerable burden on the affected families because patients have the worst experience in terms of loss of social and economic opportunities, and of medical care as assessed by a questionnaire to 2500 patients with chronic diseases (8·2% of which were Rare Diseases)[21].

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[14] No authors. Drugs for rare diseases:mixed assessment in Europe. Prescrire Int. 2007;16(87):36-42.
[15] HEALTH INDICATORS FOR RARE DISEASES:State of the Art and Future Directions. First Report. June 2008
[16] A new era of hope for the world's most neglected diseases. PLoS Med. 2005;2(9):e323.
[17] Fehr A, Thürmann P, Razum O. Editorial drug development for neglected diseases a public health challenge . Trop Med Int Health. 2006;11(9):1335-8.
[18] Rinaldi A. Adopting an orphan . Incentives to develop drugs for rare disorders raise hopes and controversy. EMBO Rep. 2005;6(6):507-10.
[19] Schieppati A, Henter JI, Daina E et al. Why rare diseases are an important medical and social issue? Lancet 2008; 371: 2039-41.
[20] Eguale T, Bartlett G and Tamblyn R. Rare visible disorders/diseases as individually identifiable health information. AMIA Annu Symp Proc. 2005;2005:947.
[21] Van Weely S, Leufkens HGM. Orphan diseases. Background paper. In:priority medicines for Europe and the world. A public health approach to innovation. http://mednet3.who.int/prioritymeds/report/index.htm#c

Moreover, Rare Diseases substantially affect life expectancy as confirmed by a prospective study, which revealed that only 11% of newborn babies with internal metabolic problems, go on to reach adulthood[22].
The category of Rare Diseases, which tends to become a by-product of the Orphan Drugs status, is a boundary object from the marketing & socio-historical perspective[23]. As such, it has different specific understandings: it relates to the patients' experience of illness, it is a miscellaneous category for physicians, whereas the pharmaceutical industry first considered it as being synonymous with niche markets, firstly with an innovation driver and then with a profitable equity segment. Nevertheless, patients suffering from those Rare Diseases share the same difficulties in obtaining an accurate diagnosis, adequate information about the disease, access to qualified specialists, and dedicated therapeutic strategies along with relevant drugs. Each of those topics being relevant opportunities for marketers in terms of Disease Awareness Campaigns, Continuing Medical Education and Brand Mix Marketing. Indeed successful translation of Rare Diseases research into an Orphan Drug discovery and its development program is dependent on the disease class, its prevalence and the disease-specific scientific output[24]. For the period between2008 and 2013, the Commission has adopted a White Paper "Together for Health: A Strategic Approach for the EU 2008-2013" establishing a second program initiative in order to prevent and treat specific diseases, including genetic disorders, and to promote action on the prevention of Rare Diseases, which are explicitly mentioned. Rare Diseases are now one of the priorities in the second program of Community action in the field of health[25,26].

Epidemiology of Rare Diseases

There is very little documented information on the epidemiology of Rare Diseases, however, it is important to estimate the total number of people affected and the prevalence per disease. The natural history of Rare Diseases must be assessed in order to adapt care and monitor improvements. The exact prevalence rate is difficult to obtain from the available data sources and there is little consistency between studies and poor documentation of the methods used. Often, the studies confuse incidence and prevalence as well as incidence at birth and lifelong incidence[27].
The absence of a universally recognised coding system is an obstacle for reliable registration of patients in national or international databases, preventing assessment of the economic and social effects of Rare Diseases. As an example, even though it is used in most countries, it is not possible to use the International Classification of Diseases (ICD) for Rare Disease monitoring[28]. To deal with this issue, the European Rare Disease Task Force of the Health and Consumers Protection Directorate General of the European Commission has set up a working group to collaborate with the WHO on ICD-10, and is considering all other existing

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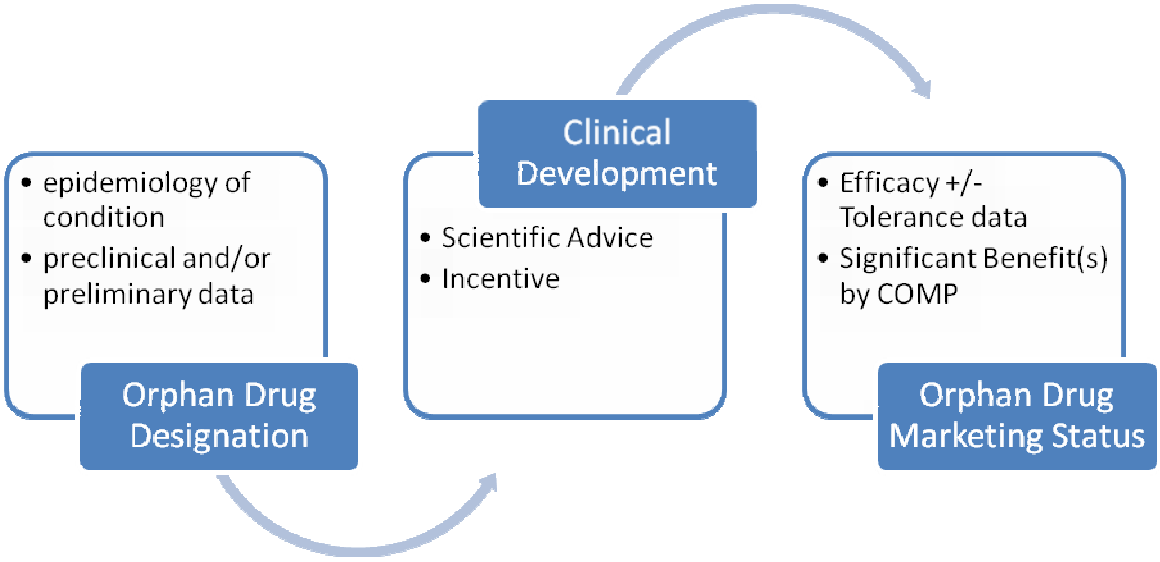
[22] Dionisi-Vici C, Rizzo C, Burlina AB, et al. Inborn errors of metabolism in the Italian pediatric population:a national retrospective survey. J Pediatr 2002;140:321–27.
[23] Huyard C. How did uncommon disorders become 'rare diseases'? History of a boundary object. Sociol Health Illn. 2009;31(4):463-77.
[24] Heemstra HE, van Weely S, Büller HA, et al. Translation of rare disease research into orphan drug development:disease matters. Drug Discov Today. 2009;14(23-24):1166-73.
[25] White Paper COM(2007) 630 final "Together for Health:A Strategic Approach for the EU 2008-2013" of 23 October 2007
[26] EU Health Strategy and the Decision No 1350/2007/EC of the European Parliament and of the Council of 23 October 2007
[27] Knight AW, Senior TP. The common problem of rare disease in general practice. Med J Aust. 2006;185(2):82-3.
[28] WHO. International Classifi cation of Diseases. 10th revision. http://www.who.int/classifi cations/apps/icd/icd10online.

classifications to provide stakeholders with a uniform system[29]. Meanwhile some Rare Diseases, national or international registries have been set up and maintained by either researchers, patients' associations, public institutions or drug companies.
Assessment of the prevalence of Rare Diseases was attempted by the European Organization for Rare Diseases (Eurordis), and Orphanet, with the support of the European Commission. Paradoxically Rare Diseases appear to be common. Estimates suggest that between 6% and 10% of the community suffer from a Rare Disease at any one time[30,31].
The 2005 Eurordis survey of 5980 patients suffering from one of eight Rare Diseases identified delayed diagnosis as a major issue: 25% of respondents reported waiting between 5 and 30 years from the onset of symptoms to a confirmed diagnosis. Forty per cent of respondents reported an initial wrong diagnosis. This resulted in inappropriate surgery (16% of respondents), medication (33%), or psychological care (10%). Forty-five per cent of respondents reported poor communication about their diagnosis[32]. Therefore, this category has been in growing use in the fields of public health and patient advocacy for the past 15 years in Europe along with the "Orphan Drug" status[33].

Orphan Drugs regulatory status

Orphan Drugs are intended to provide a benefit for the patient, this being a symptomatic relief and/or a real cure. Indeed a genetic defect can be cured if the missing enzyme secondary to the genetic defect can be supplied by recombinant DNA techniques at high levels in the milk of transgenic rabbits, as is the case with human alpha-glucosidase in Pompe's disease.
In Europe, designation as an Orphan Drug is clearly different from usual marketing authorization. The European Commission designations are based on the opinion of the Committee for Orphan Medicinal Products (COMP) within the European Medicines Agency (EMEA). The Orphan Regulation was proposed by the Commission in July 1998 and has been in force since 2000[34].

[29] Schieppati A, Henter JI, Daina E et al. Why rare diseases are an important medical and social issue? Lancet 2008;371:2039-41.
[30] Eurordis. European Organisation for Rare Diseases. What is a rare disease? http://www.eurordis.org/article.php3?id_article=252
[31] National Organization for Rare Disorders. About NORD. http://www.rarediseases.org/info/about.html
[32] Eurordis. European Organisation for Rare Diseases. EurordisCare2:survey of diagnostic delays, 8 diseases, Europe. http://www.eurordis.org/article.php3?id_article=454
[33] Huyard C. How did uncommon disorders become 'rare diseases'? History of a boundary object. Sociol Health Illn. 2009;31(4):463-77.
[34] Commission Regulation(EC) N° 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.



Criteria for the designation of an Orphan Drug are the low prevalence of the disease it intends to treat, severity of the disease and the expected significant benefit for the patients[35]. In addition, the Commission adopted the provisions for implementation of the criteria for orphan designation and defining the concepts of "similar medicinal product" and "clinical superiority"[36]. Drugs designated as Orphan Drugs are entered into the Community Register for Orphan Medicinal Products. Orphan Drugs status is a difficult tool to handle, on the marketing side, because it is an ever changing regulatory environment. Recent discussions regarding FDA assignments (October 2009) make it compulsory to create within this Agency "a review group which shall recommend to the Commissioner of FDA appropriate preclinical, trial design, and regulatory paradigms and optimal solutions for the prevention, diagnosis, and treatment of Rare Diseases", and another group that is required to do the same with respect to neglected diseases in the developing world. The previous version of the amendment stated that FDA may only establish those groups. This highlights an ongoing harmonisation process between the EMEA and the FDA regarding procedures. Therefore future Orphan Drug applications will come under increased scrutiny from specialized experts, which in turn will require a more efficient lobbying approach ahead of submission from both patient associations and Pharmaceutical Companies.

Clinical evaluation of Orphan Drugs

Beyond its specific status along with simplified scientific requirements, clinical evaluation of Orphan Drugs is hindered by the small number of patients available for clinical trials as well as the fact that there is not always a treatment to compare with. Thus, in many cases, surrogate criteria is used instead of clinical endpoints[37].
The specificity of Orphan Drugs is highlighted in a study using publicly available information to identify the approval on drugs for neurological diseases with an orphan indication (n = 19) versus a contemporary approval on drugs for neurological diseases without an orphan indication (n = 20). It appears that 100% of drugs approved without an orphan indication

[35] Enzmann H, Lütz J. European incentives for orphan medicinal products. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2008;51(5):500-8.
[36] Commission Regulation(EC) N° 847/2000 of the European Parliament and of the Council of 27 April 2000 on orphan medicinal products.
[37] No authors. Drugs for rare diseases:mixed assessment in Europe. Prescrire Int. 2007;16(87):36-42.

include at least two randomized, double-blind, placebo-controlled trials, whereas 32% of drugs with an orphan indication have at least two such trials ($p < 0.001$) and 74% have at least one ($p = 0.02$). Thirty-three pivotal trials were conducted for the 19 drugs approved with an orphan indication. Of the 33 trials, 33% do not use a placebo control, 27% are not double blind, and 12% are not randomized. Drugs approved without an orphan indication have more pivotal trials per drug (3.8 vs 1.7 trials; $p < 0.001$) and a larger mean trial size (506 vs 164 trial participants; $p < 0.001$)[38].

Safety information is even more limited at the time of approval for Orphan Drugs as a result of various factors, such as the limited number of patients in clinical trials, the quality of the clinical trials and special approval procedures. A cohort study examined publicly available data from the websites of the US and EU regulatory authorities on Orphan Drugs approved in the US and/or the EU between January 2000 and December 2007. The main outcome measures included the nature, frequency and timing of safety-related regulatory actions, defined as (I) safety withdrawals; (II) 'black-box' warnings; and (III) written communications to healthcare professionals issued by the FDA or the EMEA between January 2000 and June 2008. Ninety-five Orphan Drugs were approved during the study period (75 in the US, 44 in the EU, and 24 in both regions). Ten products (10.5%) received a safety-related regulatory action. No safety withdrawals were identified, however 4 black-box warnings and 12 written communications were . The probability of a first safety-related regulatory action for Orphan Drugs is 20.3% after 8 years of follow-up. Orphan Drugs approved by accelerated approval (relative risk [RR] 3.32; 95% CI 1.06, 10.42), oncological products (RR 7.83; 95% CI 0.96, 63.82) and products for gastrointestinal and metabolism indications (RR 10.44; 95% CI 1.25, 87.27) have a higher risk for a safety-related regulatory action. However, detection of safety issues may be complicated by the limited experience with Orphan Drugs in practical use due to the low prevalence of the diseases they are used for[39].

Orphan Drugs Market Overview

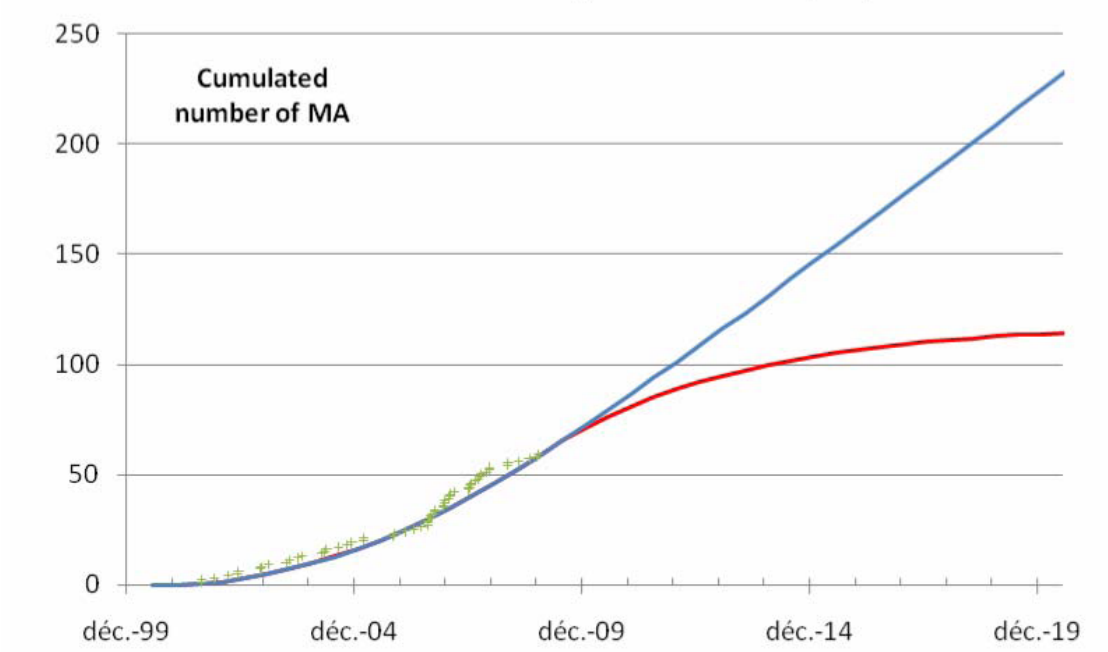
Up to mid 2010, in the USA, 2002 products have obtained Orphan Drug designation. Around 14 previously discontinued products have been recycled as Orphan Drugs. On average, products obtain 1.7 orphan designations with approximately 70% obtaining a single designation. Approximately 33% of Orphan Drugs are oncology products. At least 9% of Orphan Drugs have reached blockbuster status with two-thirds having two or more designations. An additional 25 Orphan Drugs had sales exceeding US$ 100 million in 2008 alone[40].

Experience and projections of orphan medicinal products authorised in the EU

[38] Mitsumoto J, Dorsey ER, Beck CA, et al. Pivotal studies of orphan drugs approved for neurological diseases. Ann Neurol. 2009;66(2):184-90.

[39] Heemstra HE, Giezen TJ, Mantel-Teeuwisse AK, et al. Safety-related regulatory actions for orphan drugs in the US and EU:a cohort study. Drug Saf. 2010 1;33(2):127-37.

[40] Wellman-Labadie O, Zhou Y. The US Orphan Drug Act:rare disease research stimulator or commercial opportunity? Health Policy. 2010;95(2-3):216-28.



Each cross represents actual marketing authorisations, the red line represents potential marketing authorisations for drugs designated up to December 2008, and the blue line represents the total number based on designations occurring at a rate of 80 per year, after December 2008.

Experience and projections of orphan medicinal products authorised in the EU demonstrates that it is likely that there will be about a hundred authorised drugs by 2013-2014. According to the same statistics the registration of the 100th marketing authorisation should occur in 2012 and the 200th in 2017[41].

In a context where the most common patient population size for orphan designations and approvals is fewer than 10,000 patients[42]. Similarly, during the past 9 years after the implementation of the European orphan legislation, more than 690 products have been designated and 58 have received marketing authorizations in Europe[43].

Regulatory agencies are the gateway between the Pharma/Biotech industry and patients, serving as stimulators of new drug development for Rare Diseases, as well as speeding the development process for pharmaceutical and biological agents more generally[44]. European public health measures on Orphan Drugs grants an unreserved access to the centralized procedure with a 10-year period of market exclusivity[45]. Commercial incentives, streamlined regulatory processing, exploratory trial designs, research assistance and cash infusions are all means of promoting drug development, which are being explored in the United States, Europe and beyond[46]. In order to regulate the 10-year European market-exclusivity, Article 8 in the European Orphan Drug regulation states that the marketing exclusivity period shall be reduced to six years if, at the end of five years post-introduction, the product is sufficiently profitable (although "sufficiently profitable" has not been defined by the European

[41] EURORDIS. Orphan drugs: rising to the challenge to ensure a better future for 30 million patients in Europe. October 2009.

[42] Braun MM, Farag-El-Massah S, Xu K, et al. Emergence of orphan drugs in the United States:a quantitative assessment of the first 25 years. Nat Rev Drug Discov. 2010;9(7):519-22.

[43] Butlen-Ducuing F, Rivière F, Aarum S, et al. European Medicines Agency support mechanisms fostering orphan drug development. Drug News Perspect. 2010;23(1):71-81.

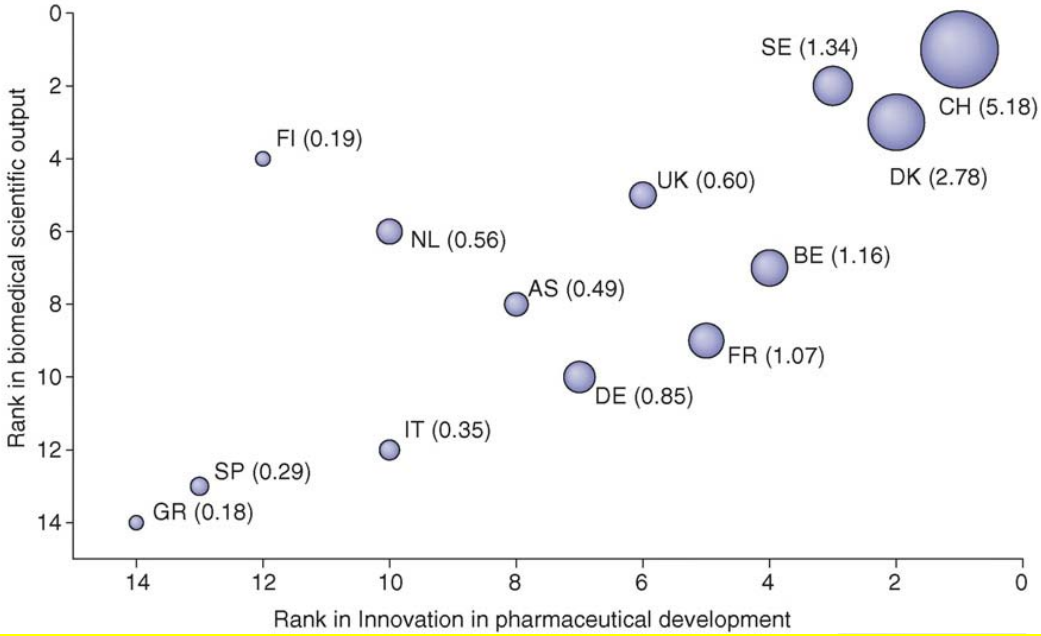
[44] Cole P. Accelerating drug development and approval. Drug News Perspect. 2010;23(1):37-47.

[45] Butlen-Ducuing F, Rivière F, Aarum S, et al. European Medicines Agency support mechanisms fostering orphan drug development. Drug News Perspect. 2010;23(1):71-81.

[46] Cole P. Accelerating drug development and approval. Drug News Perspect. 2010;23(1):37-47.

Community)[47]. On the other hand influential factors on the price setting of orphan drugs do play contributively a role but they are not fully identified so far[48].
It is rather difficult to find data at the company's level but countries' involvement has benefited from scrutiny. Denmark, Switzerland, and Sweden are among the top three for biomedical scientific output, innovation in pharmaceutical development and pharmaceutical output in terms of orphan designations. The rankings of other countries for biomedical scientific output are not always equal to their rankings for innovation in pharmaceutical development. Finland, the Netherlands and, to a lesser extent, the UK, can be identified as countries that score very well in terms of scientific output, but have not (yet) been able to translate their scientific output into innovations in pharmaceutical development and subsequently into pharmaceutical output[49].

Biomedical scientific output, innovation in pharmaceutical development and orphan designations in Europe

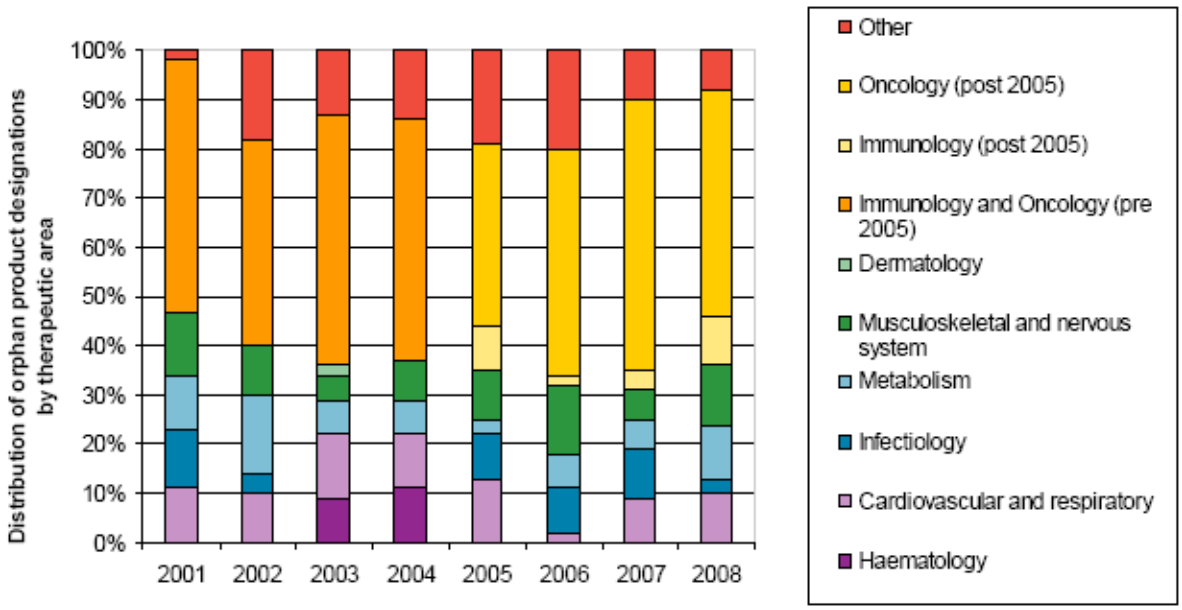


Rankings on pharmaceutical innovation performance are calculated from the integer of the combined ranking of expenditures on pharmaceutical R&D, pharmaceutical patents and pharmaceutical SMEs. Rankings for biomedical scientific output are based on the number of citations in biomedical sciences. 'Bubble' size corresponds to the standardised number of orphan designations for each country (in brackets). AS, Austria; BE, Belgium; DK, Denmark; FI, Finland; FR, France; DE, Germany; GR, Greece; IT, Italy; NL, The Netherlands; SP, Spain; SE, Sweden; UK, United Kingdom; NO, Norway; CH, Switzerland.

In terms of portfolio, most therapeutic areas have been covered by orphan product designations since the creation of COMP. This shows that the procedure is of use for very different conditions, although rare cancers do lead the way with the number of designations[50].

Evolution of the distribution of designations for orphan status by therapeutic area

[47] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products
[48] Van Ekdom L. Price Setting Orphan Drugs. Identifying the influential factors on the price setting of Orphan Drugs. MSc Thesis Science and Innovation management #0055603. Utrecht University, the Netherlands 2006.
[49] Heemstra HE, de Vrueh RLA, van Weely S et al., Orphan drug development across Europe: bottlenecks and opportunities, Drug Discov Today (2008), doi:10.1016/j.drudis.2008.05.001
[50] European Commission Evaluation of the European Medicines Agency January 2010 Final report.



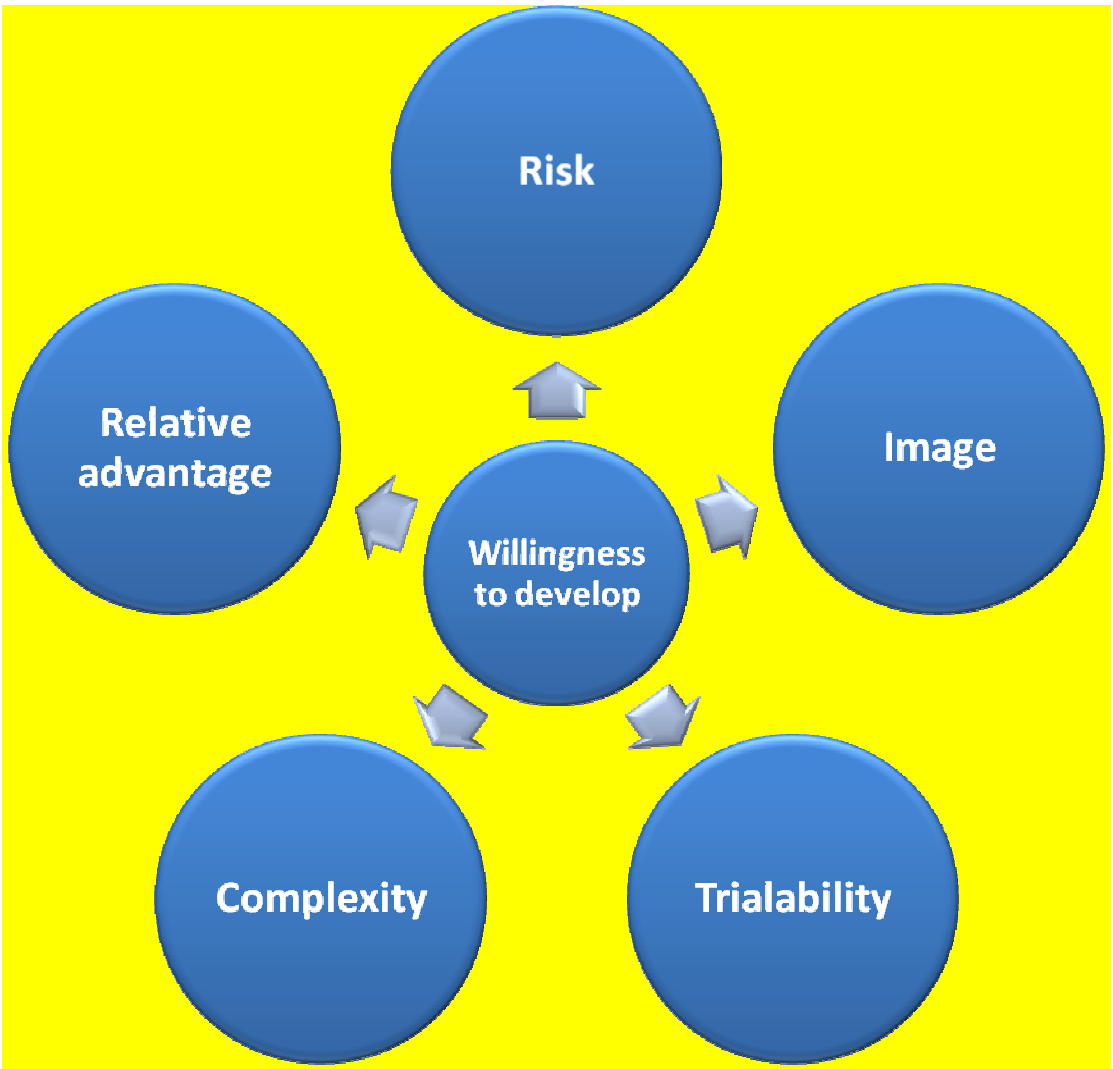
Until 2005, oncology and immunology applications are taken together, and then the figures discriminate between both, showing dominance of oncologic conditions

Reasons for success or failure of Market access are discussed below under the Key Success Factors for approval paragraph.

Orphan Drugs potential limitations

Regarding Orphan Drugs, there are three healthcare interest groups, namely the Pharmaceutical Companies, Healthcare regulatory/payers and Patients. In 2010, numerous pharmaceutical companies made the choice to invest in Orphan Drugs (see Chart F in the Appendix), some of them like BMS or Lilly because it's a way to respond to their corporate commitment as well as a way to develop their portfolio. Some companies like Swedish Orphan Biovitrum were created for the unique purpose of developing and marketing Orphan Drugs and others such as Biocodex because scholars came to them with a project they decided to support all the way down to patient prescription. All of these pharmaceutical companies made the choice to benefit from the incentives provided by the EU and, as previously stated; hundreds of Orphan Drugs are under development. Therefore, it seems that the 5 parameters that best analyse the willingness of Pharmaceutical Companies to develop Orphan Drugs are at optimal levels[51]:

[51] Moors EHM, Faber J, Hekkert MP et al. Innovation system barriers in orphan drugs development within the Netherlands. 10th international conference of the Greening of Industry Network. June 23-26 2002, Göteborg, Sweden.



- Risk is related to financial risk, which is indicated by: the cost of research into the pathogenesis of an orphan disease, the cost of developing an orphan drug (drug design, drug production, animal models, pre-clinical and clinical tests, registration and monitoring), expected revenues (number of patients, insurance payments of costs of use) and expected profitability (returns on investments). Another indicator of risk concerns the realization of the juridical benefits allowed by the EODR, namely achieving the OD-status.
- Relative advantage has been put into operation by two sets of indicators. The first set of indicators concerns the degree of correspondence between orphan drug development and conventional drug development by pharmaceutical companies, namely the scale of production and servicing market niches. The second set of indicators concerns the stimulating activities induced by the government, namely providing clinical research assistance, facilitating registration and granting market exclusivity.
- Image is conceived to be indicated by actual orphan drug development by pharmaceutical companies and their cooperation on orphan drug development with academic hospitals, patients' organizations and the regulators.
- Complexity is indicated by the amount of available knowledge on the pathogenesis of orphan diseases, available animal models, measures for financial support and registration procedures, together with the degree of sharing this knowledge among the three actor groups producers, consumers and regulators.

- Trialability is measured on the possibilities to conduct clinical trials and the cooperation of patient organizations in these trials.

Future potential limitations from Pharmaceutical Companies will come from market saturation as a result of a plethoric offer in some segments and the inevitable arousal of generic competition soon to follow.

On the other hand, Healthcare regulatory/payers are already developing potential limitations. In 2005, the NICE pointed out that Special status for orphan drugs in resource allocation will avoid difficult and unpopular decisions, however it may impose substantial and increasing costs on the healthcare system[52].

Reimbursement schemes which usually rely on the proof of short-term treatment effectiveness may potentially discriminate against slowly progressive patients, as health gain can often not be confirmed over a short period of time in these specific patients. In at least one study, inclusion and exclusion criteria for treatment appear arbitrary and may contribute to the exclusion from treatment of patients who could benefit in the long term[53]. In addition, reimbursement of Orphan Drugs can reach up to 5% of the hospital pharmaceutical budget of a given country[54]. As an example, enzyme replacement therapy can reach an annual treatment cost from anywhere between 150,000 and 450,000 € per patient[55,56].

On the other hand, assessment of the variability in use of Orphan Drugs in different healthcare systems of the European Union (Austria, Denmark, Finland, Portugal, Netherlands, and Sweden) found that it appears to be comparable to the other newly authorised drugs. No association between orphan medicine status and variability in use across countries was found ($P = 0.52$). Orphan Drugs are more expensive and have a higher innovation score than drugs without an Orphan Drug status. This means that, although strong heterogeneity in access may exist, this heterogeneity is not specific for Orphan Drugs[57].

The above data reveals that despite health authorities concerns, Orphan Drugs behave like other drugs when they enter into the market. Surprisingly enough, despite numerous publications, the question concerning the cost of untreated patients in the community in general and to the healthcare system in particular, is not addressed by the different publications on that matter.

In the end, Patients are so demanding and in the dire need of solutions that they do not develop potential limitations but rather create a huge “pull” momentum.

Key Success Factors for approval

The global average of authorised Orphan Drugs receiving approval from the CHMP is roughly 12,5 per year during the 2001-2008 period (range: 7-18, vs. only 2 in 2000). It is interesting to note that very few negative opinions have been given by the COMP whereas the

[52] McCabe C, Claxton K, Tsuchiya A. Orphan drugs and the NHS should we value rarity? BMJ. 2005;331(7523):1016-9.

[53] Schlander M, Beck M. Expensive drugs for rare disorders:to treat or not to treat? The case of enzyme replacement therapy for mucopolysaccharidosis VI. Curr Med Res Opin. 2009;25(5):1285-93.

[54] Denis A, Mergaert L, Fostier C, et al. Orphan diseases and orphan medicines:a Belgian and European study. J Pharm Belg. 2009;(4):131-7.

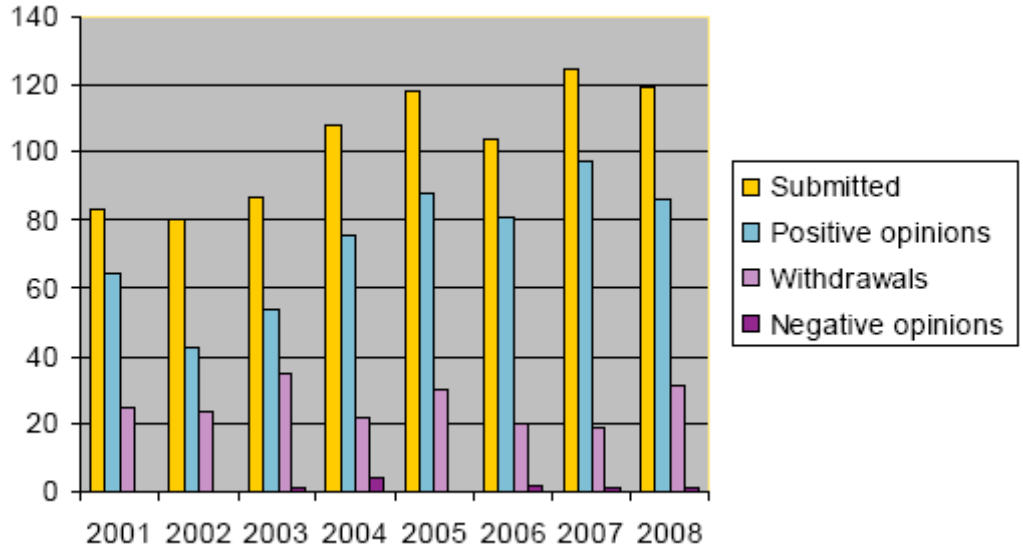
[55] Schlander M, Beck M. Expensive drugs for rare disorders:to treat or not to treat? The case of enzyme replacement therapy for mucopolysaccharidosis VI. Curr Med Res Opin. 2009;25(5):1285-93.

[56] Burls A, Austin D, Moore D. Commissioning for rare diseases view from the frontline. BMJ. 2005;331(7523):1019-21.

[57] Stolk P, Heemstra HE, Leufkens HG, et al. No difference in between-country variability in use of newly approved orphan and non- orphan medicinal products--a pilot study. Orphanet J Rare Dis. 2009 14;4:27.

number of withdrawals is relatively high (generally because the medicine would not fit appropriately the orphan designation criteria)[58].

Evolution of the number of submissions for orphan product designation and COMP opinions from 2001 to 2008



Down the stream, Orphan Drug approval is strongly associated with previous experience of the promoter in obtaining approval for another Orphan Drug (OR = 17.3, 95% CI = 5.6-53.1). Furthermore, existing synthetic entities compared to biotechnology products tend to have a higher likelihood of reaching approval status (OR = 3.9, 95% CI = 0.9-16.6)[59].
Factors associated with the success of Market Authorisation Applications for Orphan Drugs submitted to the EMEA, with added emphasis on the Scientific Advice given by the Committee for Human Medicinal Products, have benefited from a thorough analysis. Out of 188 of the Market Authorisation Applications submitted to the EMEA between 1 January 2004 and 31 December 2007, 72.9% were approved, whereas 27.1% were not approved or were withdrawn by the company. To clarify, there were 138 Market Authorisation Applications for non-orphan and 50 for orphan drugs. 58% of the latter were approved by the EMA. In the simple logistic regression analysis, company size (odds ratio (OR) 2.96, 95% confidence interval (CI) 1.92; 4.56, $p < 0.0001$) is positively correlated with a positive outcome, whereas Orphan Drugs status (Orphan Drug vs. drugs without an orphan medicine status: OR 0.38, 95% CI 0.19; 0.77, $p = 0.0067$) is negatively correlated. In total 31.4% of the Market Authorisation Applications obtain Scientific Advice related to one or more of the three critical variables. Thirty-nine of these were deemed to be compliant with Scientific Advice. Obtaining a Scientific Advice per se is not associated with outcome (Scientific Advice vs. No Scientific Advice: OR 0.96, 95% CI 0.49; 1.88, $p = 0.92$), but complying with Scientific Advice is significantly associated with positive outcome (compliant with Scientific Advice vs. no- Scientific Advice: OR 14.71, 95% CI 1.95; 111.2; non-compliant with Scientific Advice vs. no Scientific Advice: OR 0.17, 95% CI 0.06; 0.47, $p < 0.0001$). Stepwise regression analysis reveals that company size and Scientific Advice compliance are independent predictors of outcome. The proportion of the Market Authorisation Applications that receives Scientific Advice increased from 22% in 2004 to 47% in 2007. Company size

[58] European Commission Evaluation of the European Medicines Agency January 2010 Final report
[59] Heemstra HE, de Vrueh RL, van Weely S, et al. Predictors of orphan drug approval in the European Union. Eur J Clin Pharmacol. 2008;64(5):545-52.

and product type are associated with the frequency of requesting Scientific Advice (26%, 33% and 46% for small, medium-sized and large companies, respectively; 16%, 39% and 48% for known chemical substances, new chemical substances and biologics, respectively). Factors related to compliance with Scientific Advice are company size and Orphan Drugs status (25%, 60% and 84% for small, medium-sized, and large companies, respectively; 77% and 38% for drugs without an orphan medicine status and Orphan Drugs status, respectively). The strong association between company size and outcome suggests that resources and experience in drug development and obtaining regulatory approval are critical factors for a successful Market Authorisation Application. In addition, obtaining and complying with Scientific Advice appears to be a predictor of outcome[60].
Those findings confirm that Orphan Drugs benefit from their specific regulatory path but that, in addition, fundamental skills such as Drug design and development as well as drug advocacy to health authorities is mandatory.

Key Success Factors for market development

Patient power

The original impetus for Rare Diseases and Orphan Drug development came from patients seeking access to drugs that, without a focus on Rare Diseases, lacked regulatory approval or commercial viability[61]. Patient organisations are therefore a surrogate pressure group for influencing prescribers, policy makers and regulatory agencies on access to and use of pharmaceutical companies' drugs[62],[63],[64]. Patient associations encourage patients and their carers to ask questions, and assist them with self-care and decision making. They do support families by contributing to the physical, emotional, psychological, spiritual, and social needs of the patient's support network. Among those needs, supporting the patient's journey through social service and medical bureaucracies, and interpreting written and verbal information are critical. Patients trust these organisations to act on their behalf in an unbiased manner[65]. In that respect, the internet offers a highly valuable opportunity for those with Rare Diseases to connect with, learn from, and provide support to others having similar experiences. Patient Associations like the Primary Biliary Cirrhosis Organization (PBCers) provides an electronic mailing list and informational resources for those who have this autoimmune liver disease. Messages exchanged on this particular mailing list have a biomedical – such as health care providers (32.7%), medications (30.9%), tests and procedures (25.8%), and symptoms (25.7%) – rather than socio-emotional or organizational emphasis[66]. The annual awareness-raising event "Rare Disease Day", co-ordinated by EURORDIS at the international level and National Alliances of Patient Organisations at the national level, is typically an example of rising patient power. Since pharmaceutical companies and patient organisations share common interests, funding relationships have been developed[67]. The notable relationship between Pharmaceutical companies and patient associations is strictly regulated.

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[60] Regnstrom J, Koenig F, Aronsson B, et al. Factors associated with success of market authorisation applications for pharmaceutical drugs submitted to the European Medicines Agency. Eur J Clin Pharmacol. 2010;66(1):39-48.
[61] Knight AW and Senior TP. The common problem of rare disease in general practice. MJA 2006;185(2):82-83.
[62] Medawar C: Promotion of prescription drugs: trade tactics? Consumer Policy Review 2002, 12:18-30.
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[64] Buckley J: Pharmaceutical Marketing – Time for Change. Electron J Bus Ethics Org Stud 2004, 9:4-11.
[65] Hirst J: Charities and patient groups should declare interests. BMJ 2003, 326:1211.
[66] Lasker JN, Sogolow ED, Sharim RR. The role of an online community for people with a rare disease content analysis of messages posted on a primary biliary cirrhosis mailinglist. J Med Internet Res. 2005;7(1):e10.
[67] Traulsen JM, Almarsdottir AB: Pharmaceutical policy and the lay public. Pharm World Sci 2005, 27(4):273-7.

A 2010 symposium on Dravet's syndrome in Italy (a dreadful epileptic encephalopathy) highlighted the fact that now patient associations not only provide support and lobbying pressure but are becoming contributors to the knowledge management of the disease of their beloved ones. From that point of view, the work of the IDEA League Family Network produced a truly scientific contribution to the study of Sudden Unexpected Death in Epilepsy (SUDEP)[68] affecting Dravet's patients, which deserved public communication during this international scientific symposium along with usual Key Opinion Leaders.
Beyond regulatory compliance, patient power is one of the major Key Success Factor's of the Orphan Drug market. To be appropriately addressed, it requires a deep understanding of the real distress of patients' families who seek mutual support and better understanding from the healthcare community.

Key Opinion Leaders

Key Opinion Leaders (KOLs) also deserve special attention. KOLs are known to be influential on a regional, national or international level and their support for evidence is sufficient endorsement to consider adoption[69]. According to the Hiss construct[70], KOLs are physicians who (I) encourage learning and enjoy sharing their knowledge; (II) are clinical experts and always seem to be up-to-date and (III) treat others as equals[71]. Beyond their essential undergraduate training role regarding Rare Diseases, they endorse professional media content including the internet, which is considered to be the best way to obtain data to optimize criteria for Rare Disease patient referral by Primary Care Physicians[72].
Moreover, grouping KOLs with International Expert Groups is necessary because of the limitations of the Evidence Based Medicine (EBM) concept in the Rare Disease sphere. EBM - usually seen as the gold standard for determining pharmacological choices in human medicine - is based on the assumption that randomised placebo-controlled, double-blinded clinical trials are the sole source of objective data on the safety and effectiveness of any clinical intervention[73]. But in Rare Diseases there is a paucity of information from these complex and time consuming studies. With this specific context, International Expert Groups can enrich the EBM approach with the Considered Therapeutic Decisions concept and elicit consensus guidelines according to the AGREE methodology[74].
Key Opinion Leaders do not behave in the usual way when they are involved in an Orphan Drug project. This has to be taken into account when planning any Medical Education (MEDED) program or designing any kind of road show. Their vision and perception of their patients' needs is broadening. Thus they expect their marketing contacts to increase the range

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[68] Watts KP, Skluzacek JV, Goodliffe SE. Mortality and SUDEP in Dravet Syndrome: Information from Families for Doctors. Dravet Syndrome – Severe Myoclonic Epilepsy of Infancy:30 Years Later. Verone Italy, 2009. Idea League Poster

[69] Lococ L, Dopson S, Chambers D, Gabbay J: Understanding the role of opinion leaders in improving clinical effectiveness. Soc Sci Med 2001, 53:745-757.

[70] Hiss RG, MacDonald R, Davis WK: Identification of physician educational influentials (EI's) in small community hospitals. In Proceedings of the seventeenth annual conference on research in medical education Washington, DC; 1978:283-288. Ref Type: Conference Proceeding

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[72] Avellaneda Fernández A, Izquierdo Martínez M, Luengo Gómez S, et al. [Need for primary care training in rare diseases]. Aten Primaria. 2006 15;38(6):345-8.

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of their support beyond the scientific approach of the drug and its pharmacological properties. In fact they expect marketers to help them learn how to offer a more global approach beyond therapeutics including, "how to help me organise my patients' home and community". The risk being that, patient associations will appropriate this territory for themselves if marketing teams do not invest it. This would lead to the loss of many opportunities to build useful brand services (which normally build robust brand loyalty).

Role of General Practitioners

Rare Diseases can be divided into two categories: those which benefit from an immediate specialist's care (because they are diagnosed at a neonatal stage or because the first outcome is dramatic enough to address patients to specialty wards); thosewhose first outcome or calling symptoms are more insidious and/or confusing thus elicit a longer process before the accurate diagnosis is made. In this case patients will present their symptoms first to a General Practitioner.

Because General Practitioners' clinical judgment about patients is intuitive, probabilistic, and reiterative thus subjective and context dependent – in other words of "bayesian" nature –, it is considered as a clear advantage when diagnosing Rare Diseases[75,76]. Moreover, General Practitioners feel that as the physician in charge of a patient with a Rare Disease, it is their duty to do the best they can for that individual, irrespective of its effect on other patients[77]. Patients will also attend a General Practitioner in between visits to the specialist where they will require diagnosis and treatment of common ailments, and will benefit from the preventive health services offered by general practices[78]. Therefore, General Practice, as a specialty, has the opportunity to develop a generic approach to the common problem of Rare Diseases with the support of the Pharmaceutical Companies marketing Orphan Drugs and other stakeholders. This is possible because General Practitioners frequently see rare conditions (because the diagnostic is rare or because the clinical outlook is unusual), they know how to negotiate uncertainty and have a solid expertise in managing chronic disease[79,80,81,82]. They provide accessible, relationship-based advocacy and support role that is at the heart of good general practice. A thoughtful, proactive, ongoing response in the context of a continuing relationship with a General Practitioner may reduce many of the negative experiences of patients with Rare Diseases. In addition, General Practitioners need "up to date" information and CME regarding the Rare Diseases and Orphan Drugs of their patients in order to deliver appropriate care to other health issues including unrelated common conditions and preventive activities (i.e. immunisation, screening and health promotion). The CME program either delivered by Pharmaceutical Companies or Health Authorities should cover natural history, evidence-based treatment options including interaction with unrelated conditions treatments, systematic long-term care, associated problems, genetics and any relevant topic.

The need for support from Communication specialists comes from the fact that, for any given General Practitioner, in his/her entire practice, he/she will face one to two Orphan Diseases.

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[75] Chitty RN. Why clinicians are natural Bayesians is there a bayesian doctor in the house? BMJ. 2005;330(7504):1390.

[76] Gill CJ, Sabin I, Schmid CH. Why clinicians are natural bayesians. BMJ 2005;330:1080-3.

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The challenge is therefore to build a MEDED strategy that is versatile enough to respond to this major challenge.

European Lobbying

In that respect, one of the future challenges of Orphan Drugs is the way in which stakeholders are going to justify giving out special treatment with the costs of production and the value of innovation whilst arguments concerning the measurement and evaluation of health outcomes tend to apply equally to orphan drugs and drugs for more common conditions. In a context where health authorities tend to consider that valuing health outcome more highly for rare conditions is incompatible with other equity principles and theories of justice[83].
Then again, Pharmaceutical companies should build their own Lobbying strategy as a group but also as individuals in order to address this issue along with patient associations. Pharmaceutical companies need their own Lobbying strategy because their goals are superimposed on those of patient associations and because patient associations' Lobbying techniques are not adapted to Pharmaceutical standards and resources.

Development Model

The story of stiripentol makes a perfect model for Orphan Drug development as it was initiated by an academic research group led by Pr O Dulac & Dr C Chiron in cooperation with BIOCODEX. This Pharma Company provided sufficient funding to run several pivotal phase II and III clinical studies, which were published in high standard publications such as the Lancet[84]. It is worth reading in the editorial of the November 2000 issue that this commitment was a case study on "how to best serve children" as well as the fact that BIOCODEX was granted the French 2008 "Medicines for Rare Disease" GALIEN award. Moreover, in direct line with its commitment, BIOCODEX has been developing an innovative MEDED program including multimedia educational initiatives endorsed by the European Paediatric Neurology Society.

Discussion

The overall picture of Rare Diseases as a whole is that the global prevalence is similar to that of type 2 diabetes mellitus[85]. This tells us that although scattered, the Rare Disease market is huge and economically relevant. Similarly, some of the frequent diffuse parenchymal lung diseases familiar to any healthcare professional, such as sarcoidosis, hypersensitivity pneumonitis and idiopathic pulmonary fibrosis comply with the definition of a Rare Diseases in Europe, although not considered as such, because they affect less than one in every 2,000 people[86].
The kind of strategy that applies to Orphan Drugs depends on the Orphan Drug itself:

- Monopolistic i.e. the only Orphan Drug indicated for a given Rare Disease
- Competitive i.e. other Orphan Drugs are indicated for the same Rare Disease
- Unique indication i.e. the Orphan Drug is indicated for a given Rare Disease (or part of a Rare Disease) only
- Large indication i.e. the Orphan Drug is indicated for many Rare Diseases

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[83] McCabe C, Claxton K, Tsuchiya A. Orphan drugs and the NHS should we value rarity? BMJ. 2005;331(7523):1016-9.
[84] Chiron C, Marchand MC, Tran A et al. Stiripentol in severe myoclonic epilepsy in infancy : a randomized placebo-controlled syndrome-dedicated trial (STICLO study Group). Lancet 2000;356:1638-42.
[85] Knight AW and Senior TP. The common problem of rare disease in general practice. MJA 2006;185(2):82-83
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The kind of strategy that applies to Orphan Drugs depends also on maturity of the market:

- Rare Disease awareness level i.e. how familiar are stakeholders with the Rare Disease prevalence and calling symptoms
- Treatment awareness level i.e. how familiar are stakeholders with the available therapeutic options

From those parameters it is possible to draft a relevant strategy based on classic healthcare approaches. Surprisingly those who market orphan drugs often limit their strategic option because they fear that financial limitations will negatively impact the outcome. This is neglecting the fact that the critical step regarding potential financial limitation is the tactical translation of the Strategy. Indeed, further down the process, Strategy translates into Tactics, which deal with detailed manoeuvres to achieve objectives set by Strategy. Tactics adapt to the limitations of the organisation (size, resources) and respond to the environmental changes (market shifts and drifts).
Tactics are conditioned by the problems faced by patients with Rare Diseases and their families, which are essentially, a lack of available resources to the correct diagnosis; a lack of information; a lack of scientific knowledge; a lack of appropriate quality healthcare; inequalities in treatment and care and lack of understanding of social consequences. Each of those problems offers opportunities for an effective marketing mix and plan of action.
Another concept that impacts the financial limitation is the Brand. The Brand concept is not limited to a name given to a product or service, it is the aesthetic – which is the "beauty" experienced by the target audience in a philosophical sense – in other words, it is a construction of the mind that adds qualities to the product or service to give pleasure to the senses of the target audience and position the product or service as an outstanding example of its kind. A Brand that is appropriately designed, can overcome any market barrier and competition challenge whilst minimizing the financial impact, the need to build a strong Brand hasn't arisen because competition with other Orphan Drugs is low. But, like the Generic market, this will change in the near future.

Conclusion

Drug development to treat a substantial number of affected patients needs to be boosted by public and private initiatives because today almost all the Rare Diseases still have no cure. Relevant Marketing and Communication Strategy is key to achieve this goal as much as the advances in our understanding of mechanisms of many diseases and the explosion of knowledge in genetic medicine.
All of the above specificities deserve expertise and skills to be driven in a synergistic way with appropriate brand strategy. Expertise comes from experience and consultancy firms dealing with Orphan Drugs, who can certainly increase marketing teams'. With the appropriate partner, managing an Orphan Drug becomes a wonderful opportunity because it allows us to combine the personal achievement of marketing teams (e.g. elicit direct health improvement on a targeted population within a time frame compatible with professional life time in a given company) whilst still meeting corporate expectations (e.g. improve corporate brand image while cutting down development and trade costs although preserving/increasing turnover objectives).
In the near future, pharmaceutical companies will have to adjust their corporate strategy regarding Orphan Drugs with two extremes to consider: the BIOCODEX posture which concentrates on one Rare Disease with a niche strategy and the SWEDISH ORPHAN DRUG posture which tends to cover the broadest portfolio. Again, the appropriate partner will

become essential to make the appropriate choice with the relevant strategy. This approach is yet to be explore because no clear strategy has been elaborated yet.

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Conflict of interest

StratAdviser France contracted with BIOCODEX and Dr Jan-Cedric Hansen contributed personally in the elaboration of the highlights of the 2009 Severe Myoclonic Epilepsy of Infancy: 30 Years Later symposium.

Role of the funding source

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Apendix

Chart A

First Author	Title	Publication	Publication date
Pàmpols Ros T	[The ethical aspects of population screening programme of Rare Diseases][87]	Rev Esp Salud Publica	2010
Brekke M	[Rare conditions are rare][88]	Tidsskr Nor Laegeforen	2009

[87] Pàmpols Ros T, Terracini B, de Abajo Iglesias FJ, et al. Comité de Etica, Instituto de Investigación de Enfermedades Raras. [The ethical aspects of population screening programme of rare diseases]. Rev Esp Salud Publica. 2010;84(2):121-36.

[88] Brekke M. [Rare conditions are rare]. Tidsskr Nor Laegeforen. 2009 17;129(24):2615-6.

First Author	Title	Publication	Publication date
Stolk P	No difference in between-country variability in use of newly approved orphan and non- orphan medicinal products--a pilot study[89]	Orphanet J Rare Dis	2009
Price VE	Measuring disease-specific quality of life in rare populations: a practical approach to cross-cultural translation[90].	Health Qual Life Outcomes	2009
Nakao K	Strategy for translational research and breakthroughs for common human diseases using excellent animal models and rare human diseases[91].	Endocr J	2009
González-Lamuño D	[When Rare Diseases become urgent: inborn errors of metabolism in primary care][92].	Aten Primaria	2009
Vickers AJ	The clinically-integrated randomized trial: proposed novel method for conducting large trials at low cost[93].	Trials	2009
Richesson RL	An automated communication system in a contact registry for persons with Rare Diseases scalable tools for identifying and recruiting clinical research participants[94].	Contemp Clin Trials	2009
Roalfe AK	Standardisation of rates using logistic Regression a comparison with the direct method[95].	BMC Health Serv Res	2008
Seoane-Vazquez E	Incentives for orphan drug research and development in the United States[96].	Orphanet J Rare Dis	2008

[89] Stolk P, Heemstra HE, Leufkens HG, et al. No difference in between-country variability in use of newly approved orphan and non- orphan medicinal products--a pilot study. Orphanet J Rare Dis. 2009 14;4:27.
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[94] Richesson RL, Lee HS, Cuthbertson D, et al. An automated communication system in a contact registry for persons with rare diseases scalable tools for identifying and recruiting clinical research participants. Contemp Clin Trials. 2009;30(1):55-62.
[95] Roalfe AK, Holder RL, Wilson S. Standardisation of rates using logistic Regression a comparison with the direct method. BMC Health Serv Res. 2008;8:275.
[96] Seoane-Vazquez E, Rodriguez-Monguio R, Szeinbach SL, et al. Incentives for orphan drug research and development in the United States. Orphanet J Rare Dis. 2008;3:33.

First Author	Title	Publication	Publication date
Mrsić M	Rare Diseases in Croatia--lesson learned from Anderson-Fabry disease[97].	Croat Med J	2008
Kenny TD	Monitoring clinical quality in Rare Disease services--experience in England[98].	Orphanet J Rare Dis	2008
Ponder M	Genetic research on rare familial disorders consent and the blurred boundaries between clinical service and research[99].	J Med Ethics	2008
Plummer M	Penalized loss functions for Bayesian model comparison[100].	Biostatistics	2008
Van Meter KC	A procedure to characterize geographic distributions of rare disorders in cohorts[101].	Int J Health Geogr	2008
Chow SC	Adaptive design methods in clinical trials - a review[102].	Orphanet J Rare Dis	2008
Heemstra HE	Predictors of orphan drug approval in the European Union[103].	Eur J Clin Pharmacol	2008
Gaite L	[Needs in Rare Diseases during paediatric age][104].	An Sist Sanit Navar	2008
Del Barrio J	[Infrastructure and resources of social, educational and health support in Rare Diseases][105].	An Sist Sanit Navar	2008
Aldamiz-Echevarría L	[On-line resources in dealing with Rare Diseases][106].	An Sist Sanit Navar	2008
Nagore Induráin C	[The pharmacist, Rare Diseases and orphan medicines][107].	An Sist Sanit Navar	2008

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González-Lamuño D	[Rare Diseases in paediatrics][110].	An Sist Sanit Navar	2008
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Knight AW	International conferences on Rare Diseases: initiatives in commitment, patient care and connections[115].	Med J Aust	2007
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Stakisaitis D	Access to information supporting availability of medicines for patients suffering from Rare Diseases looking for possible treatments the EuOrphan Service[120].	Medicina (Kaunas)	2007
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Senior TP	Rare Diseases need a generic approach[124].	BMJ	2006
Dear JW	Are Rare Diseases still orphans or happily adopted? The challenges of developing and using orphan medicinal products[125].	Br J Clin Pharmacol	2006
Stolk P	Rare essentials drugs for Rare Diseases as essential medicines[126].	Bull World Health Organ	2006
Reidenberg MM	Are drugs for Rare Diseases "essential"?[127]	Bull World Health Organ	2006
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Chitty RN	Why clinicians are natural Bayesians is there a bayesian doctor in the house?[145]	BMJ	2005
Rinaldi A	Adopting an orphan[146].	EMBO Rep	2005
Lasker JN	The role of an online community for people with a Rare Disease content analysis of messages posted on a primary biliary cirrhosis mailing list[147].	J Med Internet Res	2005
Eguale T	Rare visible disorders/ diseases as individually identifiable health information[148].	AMIA Annu Symp Proc	2005

Chart B

First Author	Title	Publication	Publication date
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Rohde DD	The Orphan Drug Act: an engine of innovation? At what cost?[155]	Food Drug Law J	2000
Thoene JG	Current status of orphan disease drug development[156].	Curr Opin Pediatr	1994

Chart C

First Author	Title	Publication	Publication date
Enzmann H	[The ethical aspects of population screening programme of Rare Diseases][157]	Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz	2008

Chart D

Promoter	Website
99nicu	http://www.99nicu.org
AIRG	http://www.airg-france.org
British Inherited Metabolic Disease Group	http://www.bimdg.org.uk/
Centre Français des Porphyries	http://www.porphyrie.net
Cystinosis Research Foundation	http://www.natalieswish.org
Cystinosis research network	http://www.cystinosis.org

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Promoter	Website
Drug database for Acute Porphyria	http://www.drugs-porphyria.com/
EuroCareCF	http://www.eurocarecf.eu
Euroglycanet	http://www.euroglycanet.org
European Cystic Fibrosis Society	http://www.ecfsoc.org/
European Porphyria Initiative	http://www.porphyria-europe.com
Eurowilson	http://www.eurowilson.org
GIS Maladies Rares	http://www.institutmaladiesrares.net
OMIM Database	http://www.ncbi.nlm.nih.gov/omim
Orphanet	http://www.orpha.net
OrphanXchange	http://www.orphanxchange.org
PDA.se	http://www.pda.se
Ramedis	https://www-bm.ipk-gatersleben.de/stable/php/ramedis/htdocs/eng/index.php

Chart E

Patient organisations	Website
Alliance Maladies Rares (France)	http://www.alliance-maladies-rares.org/
Asociacion Mexicana de Cistinosis AC (Mexico)	http://www.cystinosismexico.org/
Association Bernard Pépin pour la Maladie de Wilson (France)	http://www.abpmaladiewilson.fr
Associazione Cistinosi (Italy)	http://www.cistinosi.it
Congenital Disorders of Glycosylation CDG Family Network	http://www.cdgs.com/
Contact-a-family (UK)	http://www.cafamily.org.uk
Cystic Fibrosis Europe	http://www.cfww.org/cfe/
Cystinose Groep Nederland (the Netherlands)	http://www.cystinose.nl
Cystinose-Selbsthilfe e.V. (Germany)	http://www.cystinose-selbsthilfe.de
Eurordis	http://www.eurordis.org/sommaire.html
Federation des Maladies Orphelines (France)	http://www.maladies-orphelines.fr/
Federazione Italiana Malattie Rare - Uniamo (Italy)	http://www.uniamo.org
Italian Porphyria Patient Association (Italy)	http://www.amapo.it
National Information Centre for Metabolic Diseases Climb (UK)	http://www.climb.org.uk/
National Organization for Rare Disorders NORD (USA)	http://www.rarediseases.org/
National Urea Cycle Disorder Foundation (USA)	http://www.nucdf.org/index.htm
Primary Immunodeficiences patients IRIS (France)	http://www.associationiris.org/
The British Porphyria Association (UK)	http://www.porphyria.org.uk/
The Cystinosis Foundation (Australia)	http://australia.cystinosis.com/
The Cystinosis Foundation (France)	http://www.cystinose.org/

Patient organisations	Website
The Cystinosis Foundation (Ireland)	http://ireland.cystinosis.com
The Cystinosis Foundation (UK)	http://www.cystinosis.org.uk/
The Cystinosis Foundation (USA)	http://www.cystinosis.com
The International Pemphigus Foundation	http://www.pemphigus.org
The Wilson's Disease Association (UK)	http://www.wilsons-disease.org.uk
The Wilson's Disease Association	http://www.wilsonsdisease.org/index.html

Chart F

Pharmaceutical Industry and public/private associations	Website
Actelion	http://www.actelion.com
Allergan	http://www.allergan.com
Amgen	http://www.amgen.com
Amicus Therapeutics	http://www.amicustherapeutics.com
Ark Therapeutics	http://www.arktherapeutics.com
Baxter	http://www.baxter.com
Biocodex	http://www.BIOCODEX.com
BioMarin	http://www.bmrn.com
Bristol-Myers Squibb	http://www.bms.com
Cephalon	http://www.cephalon.com
Eli Lilly	http://www.lilly.com
European Biopharmaceutical Enterprises (EBE)	http://www.ebe-biopharma.org
European Federation of Pharmaceutical Industries and Associations (EFPIA)	http://www.efpia.org
European Rare Diseases Therapeutic Initiative (ERDITI)	http://www.erditi.org
Genentech	http://www.gene.com
Genzyme	http://www.genzyme.com
Gilead	http://www.gilead.com
Novartis	http://www.novartis.com
Pharmaceutical	http://www.phrma.org
Roche	http://www.roche.com
Seattle Genetics	http://www.seagen.com
Sigma Tau	http://www.sigmatau.com
Swedish Orphan Biovitrum	http://www.sobi.com
Zystor Therapeutics	http://www.zystor.com