

Policies for Rare Diseases and Orphan Drugs

KCE reports 112C

The Belgian Health Care Knowledge Centre

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Policies for Rare Diseases and Orphan Drugs

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Executive summary

BACKGROUND AND AIMS OF THE STUDY

Due to low prevalence, rare diseases have traditionally been neglected by industry and by the scientific, medical and political communities. It is estimated that there are currently between 5000 and 7000 different rare or rare diseases. Both in the United States (US) and in the European Union (EU), schemes were launched to stimulate the development of 'orphan drugs', drugs developed to treat these rare diseases. The rationale behind these legislations is to compensate industry for the risks and lower potential return on investment as a consequence of the inherently low number of patients. These schemes are considered as a success with an increasing number of Orphan Designation requests filed at the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Orphan Designation refers to granting the orphan status to a medicinal product, while Marketing Authorisation refers to the approval to bring the product to the market. Since the development of the regulation to promote research and development on orphan drugs in the EU in 2000, 522 drugs obtained Orphan Designation and 47 received Marketing Authorisation.

While Orphan Designation and Marketing Authorisation for these orphan drugs are decisions taken at the EU level, the drug reimbursement decision is a member state (MS) responsibility. National drug reimbursement committees (DRCs) are facing the trend of the increasing number of new orphan drugs entering the market and expect a relative increase in the budget spent on orphan drugs as compared to drugs for more common diseases mainly because of the high prices charged for these orphan drugs.

This study's objectives are to:

1. provide an overview of the commonly used definitions for 'rare diseases' and 'orphan drugs' and describe the particularities of orphan drugs as compared to drugs for regular diseases;
2. describe the regulatory processes for orphan drugs from Orphan Designation to reimbursement;
3. compare the Belgian orphan drug reimbursement policy with other countries;
4. estimate the current budget impact of orphan drugs and forecast the expected future budget impact;
5. formulate recommendations for policy makers concerning orphan drugs.

METHODS

A narrative review, based on regulatory documents and published articles, provides an overview of the definitions for rare diseases and orphan drugs. For the description of regulatory processes for orphan drugs regulatory documents were examined and interviews performed with experts and key actors involved in the processes, both at national level and at European level (EMA). Representatives of various stakeholders, including the pharmaceutical industry, patient organisations, policy makers, and experts involved in the assessment of orphan drug files were interviewed.

To examine the consistency of the information provided by industry to the different authorities at different levels and the extent to which information available at European level could be used or be made more useful for national DRCs, a comparison was made between the clinical files submitted to the EMA for obtaining marketing Authorisation, the resulting European Public Assessment Reports (EPARs) and the clinical evidence submitted to the Belgian National Institute for Health and Disability Insurance (NIHDI) as part of a drug reimbursement request. This was done for 15 specific drug-indication combinations. This collaboration between the EMA and a national Health Technology Assessment (HTA) agency was unique and shows that it can serve a mutual interest, especially concerning orphan drugs.

Additionally, a critical appraisal was made of the clinical and economic evidence submitted to the Belgian DRC for 8 cases. These were not necessarily included in the 15 cases examined at the EMEA. The critical appraisal mainly looked at the type and level of evidence submitted as well as the methodological standards applied to drug reimbursement files for orphan drugs.

Six countries were included in the cross-country comparison of orphan drug reimbursement procedures: Belgium, France, Italy, the Netherlands, Sweden and the United Kingdom. The country comparison relied on grey literature as well as on a survey among experts of the respective countries.

For all reimbursed orphan drugs in Belgium the budget impact was estimated based on information in the reimbursement request file and publicly available information. In addition, simulations of the expected future budget impact of orphan drugs were made, using as a basis the average number of orphan drugs receiving marketing Authorisation each year, the proportion of orphan drugs obtaining reimbursement in Belgium and the average yearly orphan drug cost per patient.

DEFINITIONS AND PARTICULARITIES OF ORPHAN DRUGS

In the European legislation a rare disease is defined as a life-threatening or chronically debilitating condition with a prevalence of 5 patients per 10 000 people or less. However, a variety of definitions of rare diseases and of orphan drugs is used in the legislation of various countries.

Also, a number of challenges exist with respect to the development, Marketing Authorisation, pricing, reimbursement and post-marketing follow-up of orphan drugs.

Because of the low prevalence of these diseases, the development of a treatment is usually not considered economically interesting for a company. This situation might create unequal access to treatment between patients suffering from a rare disease and patients suffering from a more common disease. Therefore, the EU has created a series of incentives for the development of orphan drugs, such as fee reductions, protocol assistance and 10 years of market exclusivity.

Orphan drugs are usually expensive. Considering all orphan drugs reimbursed in Belgium in 2008, the cost per patient per year was estimated to range from €6000 (for the treatment of gastro-intestinal stromal tumour) to €312 000 (for the treatment of mucopolysaccharidosis type I). Companies justify these high prices by claiming that the high costs of research and development for orphan drugs can only be recouped from a small number of patients by asking higher prices. An additional explanation might be the monopoly situation that emerges when there are no alternative treatments yet for a specific rare condition and when, at the same time, no Marketing Authorisation can be granted to a similar product for the same therapeutic indication. It is worth noting that some products that were originally approved as orphan drugs and as such benefited from special measures later became top sellers, either because the indications were extended to more common diseases or because the rare indication became more frequent.

ORPHAN DESIGNATION AND MARKETING AUTHORISATION

To qualify for the special regulatory arrangements for orphan drugs, a drug has to obtain the orphan status through the Orphan Designation procedure at the EMEA. Afterwards, when the drug is ready for market introduction, Marketing Authorisation can be requested. At the EMEA two separate committees are responsible: the Committee for Orphan Medicinal Products (COMP) and the Committee for Human Medicinal Products (CHMP) respectively.

Orphan Designation is subject to two conditions:

- the medicinal product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that either affects less than 5 in 10 000 persons of the Community; or that without incentives is unlikely to generate sufficient return on investment to justify the expenditure;
- there is an absence of solution or the drug brings a significant benefit compared to the present situation.

The EMEA criteria used for Orphan Designation are different from the FDA's. The FDA also considers the prevalence criterion, but more from the perspective of economic viability than from the perspective of existing alternatives. In the US, Orphan Designation cannot be reconsidered, whereas it can in the EU. The FDA grants market exclusivity for 7 years.

In contrast to many of the other drugs, where a national procedure still exists for obtaining Marketing Authorisation, since 2005 orphan drugs can only obtain Marketing Authorisation through the centralized procedure at the EMEA. A Marketing Authorisation request is assessed by the CHMP supported by the preparatory work of the rapporteurs and their teams. The CHMP gives an opinion to the European Commission, which finally decides on the Marketing Authorisation. Based on the CHMP assessment report a European Public Assessment Report (EPAR) is prepared and published on the web-site of the EMEA.

A drug cannot receive Marketing Authorisation for an rare indication *and* a non-rare indication. In case of a conflict, the rare indication has to be dropped or marketing Authorisation will have to be requested for the drug under a different name. Consequently, identical products can be brought to the market under different names and prices.

A company can decide to make a drug that has not yet obtained Marketing Authorisation but that is being considered by the EMEA, available on the market under the format of a '*compassionate use programme*'. The rules and conditions of the compassionate use programmes are organized either at the European level by the EMEA or at the national level by the individual member states.

ORPHAN DRUG REIMBURSEMENT IN BELGIUM

Drug reimbursement decisions are taken by the Minister of Social Affairs, after advice from the Drug Reimbursement Committee (DRC). Orphan drugs follow the same procedure as Class I pharmaceutical products, i.e. products for which the company claims a therapeutic added value. However, unlike for Class I pharmaceutical products, no pharmacoeconomic evaluation has to be submitted for orphan drugs. A decision on the reimbursement is taken within 180 days following the submission of the reimbursement request.

At the end of December 2008, 31 orphan drugs were reimbursed in Belgium (including two products that do not have orphan drug status, but reimbursed for an rare indication) for a total of 35 rare indications. Orphan drugs are fully reimbursed.

The prescription and individual reimbursement of orphan drugs is subject to conditions. The treating specialist physician must first obtain the approval of a Medical Advisor of the patient's sickness fund to prescribe the medicine. The Medical Advisor can, but is not obliged to, request the advice of a "College of Medical Doctors for Orphan Drugs" (CMDOD). In practice, all sickness funds have agreed to refer all requests to the CMDOD if one exists. Separate Colleges exist for separate products. It is the DRC that decides whether or not a College is established. Individual reimbursement decisions are taken on a case by case basis by the CMDOD. At the end of 2008, there were 18 colleges for 18 out of the 31 orphan drugs.

If a medicinal product is not yet on the Belgian list of reimbursed pharmaceutical products, the patient may be able to benefit from a compassionate use or medical need programs by the company or in case the drug is already available on the market, request reimbursement through the Special Solidarity Fund (SSF). Conditions for compassionate use or reimbursement through the SSF are defined by law. In 2007, orphan drugs accounted for about 35% of the SSF's total budget.

INTERNATIONAL COMPARISON

As in France, Italy and Sweden, Belgium has a number of centres of reference for rare diseases that are recognized by the NIHDI. Belgium has 8 centres for human genetics, 10 centres for monogenic metabolic disorders and 6 centres for neuromuscular disorders, although these centres are not completely comparable to the centres of excellence in other countries. However, no formal network of centres for rare diseases exists in this country. Centres of reference can build up expertise in specific rare diseases more easily than in cases where patients remain scattered over the country.

In comparison with other countries, national measures to promote research on orphan drugs are relatively limited in Belgium. Sales of orphan drugs are exempted from taxes but no formal research or support programmes are developed like in France, Italy and the Netherlands.

Most countries, except for Sweden and the UK, compare the price requested by the company to the price in other countries. This creates incentives for the companies to introduce their products first in countries where a price requested as well as reimbursement are relatively easy to obtain compared to other countries. The UK has set up a system of profit control to control prices and Sweden uses a system of negotiation at the regional level.

In Belgium and the UK, the distribution of orphan drugs occurs through hospital pharmacies only, although no formal prohibition exists against the sales of orphan drugs in open pharmacies. In the other countries orphan drugs can also be delivered through community pharmacies. In Belgium, the UK and Italy prescription of orphan medication is the exclusive responsibility of a specialist physician. In all countries, specific conditions apply to the prescription of orphan drugs. An interesting case in this respect is Italy, where an orphan drug for an individual patient can only be delivered upon registration of the treatment start and follow-up in a national disease registry.

EVIDENCE LEVELS IN REIMBURSEMENT FILES

To obtain reimbursement of an orphan drug, companies have to submit evidence on the efficacy and preferably also on the effectiveness of the drug as well as a budget impact analysis to the DRC.

The evidence on clinical effectiveness is typically limited for orphan drugs, especially for drugs targeting extremely small groups of patients. Due to the small number of patients clinical studies are rarely sufficiently powered to detect significant results on hard clinical endpoints. Moreover, the natural history of the disease is usually unknown, as physicians only have limited experience with the disease. The level of evidence in orphan drug reimbursement requests is therefore generally low. However, for nearly all products we examined at least one randomized controlled trial (RCTs) was performed demonstrating the possibility to perform RCTs for orphan drugs.

With respect to the choice of the comparator, it has been observed that alternative treatments were available for 15 orphan drugs, and that different orphan drugs sometimes have the same indication.

Budget impact analyses in drug reimbursement files are often incomplete, in that they do not account for the budgetary impact of the product in the different indications for which the product can be used. Companies can submit separate files for separate indications, in which case they calculate the budget impact of the indication for which the request is submitted, while the DRC should be able to consider the total budget impact of successive reimbursement files of an orphan drug relating to different indications. Methodological guidelines for budget impact analyses do not exist yet.

CLINICAL INFORMATION AT DIFFERENT LEVELS

The clinical file submitted to the EMEA in the context of a Marketing Authorisation request is not available for the DRCs of the member states, but a public assessment report (EPAR) is published for drugs that obtained Marketing Authorisation. The Belgian DRC asks companies to send the end-of-study reports as part of their drug reimbursement request file. Although companies are not obliged to do this, they usually provide these reports.

The information from the clinical files submitted to the EMEA is generally well-represented in the EPARs, although some suggestions could be made to further improve the utility of the EPARs for the national DRCs. For some drugs, a selective representation of the study results was found in the drug reimbursement request file: absence of the results of a negative study, of a phase I/II study and of an extension study and a vague description of the improvement without mentioning that these results were not significant from a statistical point of view. In 4 of the 15 examined cases more information was provided in the NIHDI file than was available in the EMEA file, which can be explained by the time lag between the Marketing Authorisation request and the drug reimbursement request.

Another observation is that an orphan drug may receive approval under exceptional circumstances based on surrogate endpoints only. In such cases the information included in the EPAR, may not be relevant as such for the national decision maker, since the decision maker is mostly interested in *clinically relevant* outcomes parameters. In such cases the EMEA may request an additional RCT including these hard endpoints as a postmarketing requirement. Unfortunately, the results of such studies are not always made public by the EMEA and the EPAR is not automatically updated.

BUDGET IMPACT ANALYSIS AND FORECAST

The NIHDI expenditures on orphan drugs in Belgium is estimated to have been about €66 million or over 5 % of total hospital drug budget in 2008 and further estimates indicate the future cost will be well above 10 % of hospital drug budget in five years from now. Orphan drugs represent probably 2% of total drug reimbursement expenditures by NIHDI in 2009, and are estimated to represent close to 4% in 2013.

This increasing cost creates an additional upward pressure on health care budgets and may challenge the limits of solidarity between citizens.

The high prices combined with the growing budget impact of orphan drugs also negatively affect the image of the orphan drugs among decision-makers.

RECOMMENDATIONS

EUROPEAN RECOMMENDATIONS

Disease and patient registries

- Priorities for research on rare diseases should be defined on European level in order to target public research funds for research and development of orphan drugs.
- For the high priority rare diseases, Europe should invest in setting up registries as early as possible; preferably before a drug is being developed for the disease. Data on the natural history of the disease and baseline risks are indispensable for describing the epidemiology of the disease and put into context the clinical effectiveness of a treatment. The Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data should be respected when setting up these registries and using their data.
- HTA agencies could play a role in the design of patient registries to ensure that the data collected can be used to help appreciate the effectiveness and cost-effectiveness obtained for novel drugs.
- The aggregated data from the registries should be publicly available.
- Funding and governance of the registries should be independent from the company developing an orphan drug. Innovative models combining European and national funds could be explored to set up such a system, the beneficiaries being the companies considering the clinical development of an orphan drug, the medicine agencies in assessing efficacy and safety, the national health care insurance funds, and the patients.

Orphan drug designation and marketing authorisation

- Evidence from Randomized Controlled Trials (RCTs) with clinically relevant endpoints should remain the standard for granting marketing authorization. The clinical endpoints should also have relevance for national reimbursement decisions.
- Surrogate outcome measures should only be used if there is a clear link with final endpoints or when final outcomes cannot be measured over an acceptable period of time.
- HTA agencies may provide valuable input at the EMEA level for the definition of the endpoints needed and level of clinical improvement required in phase 3 studies, such that the product would qualify for reimbursement.
- The criteria for obtaining the orphan drug status and the associated incentive mechanisms may have to be revised in order to avoid artificial sub-setting.
- The marketing exclusivity period should be revised when a product turns out to be profitable after a specific period of time, considering *all* indications of the drug. EU regulation should define what profitability means as well as the period of time over which profitability is assessed.
- The European Public Assessment Reports (EPARs) should always
 - include a standard and complete tabular overview of clinical trials which were performed or are still ongoing, mentioning the primary endpoints and the results for the pre-defined analyses, along with their level of significance
 - be updated whenever new evidence becomes available from studies requested by the EMEA in case of marketing Authorisation under exceptional circumstances.

NATIONAL RECOMMENDATIONS

Reimbursement policy

- A drug reimbursement request file for an orphan drug should contain the same elements as a reimbursement request file for a class I pharmaceutical product, more specifically:
 - At least efficacy, but preferably effectiveness, on a clinically relevant outcome should be demonstrated.
 - Cost-effectiveness ratios should be presented to show what society is paying for a Quality Adjusted Life Year (QALY) or life year gained.
 - Budget impact analysis should be based on epidemiological data from registries.
 - *Standardised* cost information submitted to the Federal Public Service Economy in the context of pricing. This standardisation has yet to be realised.

Price setting and budget impact control

- Price setting would ideally be dealt with at the European level or coordinated between member states.
- In the meantime, NIHDI might consider different options to control the prices of orphan drugs:
 - Requiring a justification for the price based on detailed information on the investments made and the potential return at a global level. This should be accompanied by a regular monitoring.
 - Risk-sharing between the drug company and the public payer, based on price for performance or conditional reimbursement. The minimally expected level of effectiveness on specific endpoints and the consequence of not realising the expected result, should be clearly specified when risk-sharing schemes are envisaged.
- If a product is already reimbursed other indications, the budget impact of the product for those indications should also be reported.

Centralisation of Prescription requests

- All requests for the reimbursement of an orphan drug for an individual patient should be submitted directly to one central counter organised by the secretariat of the DRC at the NIHDI. This secretariat needs to be reinforced if charged with this additional task.
- Reimbursement of an orphan drug for a particular patient should be conditional upon the delivery of the standardised information for the patient registry.
- For each of the orphan drugs, the secretariat composes a College consisting of a representative from the secretariat and external experts that are chosen for their expertise in the rare disease. The secretariat delivers the prescription requests to the appropriate college.
- The secretariat should make sure that the reimbursement criteria are consistently applied and should centralise the registration data of all reimbursement requests as well as the decisions of the Colleges. It should publish these data to increase the transparency of the system, conform the privacy law.
- The secretariat should also act as a coordination centre for rare diseases. It should be able to refer a physician who is faced with a patient with a rare disease to an appropriate expert or reference centre. A central website with appropriate information and links for all rare diseases and orphan drugs would be of use in this context.

Scientific Summary

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GLOSSARY

Afssaps	Agence Française de Sécurité Sanitaire des Produits de Santé	http://agmed.sante.gouv.fr/
AIFA	Agenzia Italiana del Farmaco (Italian Medicines Agency)	http://www.agenziafarmaco.it
ASMR	Amélioration du Service medical rendu (Improvement in clinical added value)	
ATC	Anatomical Therapeutic Chemical-code	
ATU	Authorisation for Temporary Usage	
AWMSG	All Wales Medicines Strategy Group	http://www.wales.nhs.uk
BNF	British National Formulary	
CBG	College ter Beoordeling van Geneesmiddelen (Dutch Medicines Evaluation Board)	http://www.cbg-meb.nl/cbg/nl
CEPS	Comité Economique des Produits de Santé (French Healthcare Products Economic Committee)	http://www.sante.gouv.fr/ceps/
CHMP	EMA Committee for Medicinal Products for Human Use	http://www.emea.europa.eu/htms/general/contacts/CHMP/CHMP.html
CMDOD	Belgian College of Medical Doctors for Orphan Drugs (College van Geneesheren voor Weesgeneesmiddelen / Collège de médecins pour des médicaments orphelins)	
COMP	EMA Committee on Orphan Medicinal Products	http://www.emea.europa.eu/htms/general/contacts/COMP/COMP.html
CPA	Dutch Committee for Pharmaceutical Aid	
DPBB	Swedish Dental and Pharmaceutical Benefits Board	http://www.tlv.se
DRC	Belgian Drug Reimbursement Commission (Commissie Tegemoetkoming Geneesmiddelen / Commission de Remboursement des Médicaments)	
DTC	Diagnosis and Treatment Combinations (the Netherlands)	
EC	European Commission	http://ec.europa.eu/
EGAN	European Genetic Alliance Network	http://www.egan.eu/
EMA	European Medicines Agency	http://www.emea.europa.eu/
EPAR	European Public Assessment Report	
EU	European Union	http://europa.eu/
Eurordis	European Organisation for Rare Diseases	http://www.eurordis.org
FDA	US Food and Drug Administration	http://www.fda.gov/
FPS	Federal Public Service (former Belgian Ministry)	
GIS	Groupe d'intérêt scientifique	
GVS	Geneesmiddelenvergoedingssysteem (Dutch Medicines reimbursement system)	
HAS	Haute Autorité de Santé (French High Health Authority)	http://www.has-sante.fr
HCIB	Dutch Health Care Insurance Board (College voor Zorgverzekeringen)	http://www.cvz.nl/
HTA	Health technology assessment	
ICER	Incremental cost-effectiveness ratio	
INAHTA	International Network of Agencies for Health Technology Assessment	www.inahta.org
MA	Marketing Authorisation	
MAH	Marketing Authorisation Holder	
MD	Medical Doctor	
MHRA	British Medicines and Healthcare products Regulatory Agency	http://www.mhra.gov.uk/
MS	(European Union) Member States	

NCG	National Commissioning Group (body of the British NHS)	http://www.ncg.nhs.uk/
NHS	National Health Service	
NICE	National Institute for Health and Clinical Excellence (UK)	www.nice.org.uk
NIHDI	Belgian National Institute for Health and Disability Insurance (Rijksinstituut voor ziekte- en invaliditeitsverzekering / Institut National d'Assurance Maladie et d'Invalidité)	www.NIHDI.be
NORD	National Organization for Rare Disorders (US)	www.rarediseases.org
OD	Orphan drug	
ODD	Orphan Drug Designation	
OOPD	Office of Orphan Products Development of the FDA	http://www.fda.gov/orphan/
ORPHANET	The portal for rare diseases and orphan drugs	www.orpha.net
PA	Protocol assistance (EMA)	http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/index.htm
PCT	Primary Care Trust (United Kingdom)	
PPRS	British Pharmaceutical Price Regulation Scheme	
QALY	Quality Adjusted Life Year	
RCT	Randomized controlled trial	
Rol	Return on Investment	
SA	Scientific advice	http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/index.htm
SAWP	Scientific Advice Working Party of the EMA	
SMC	Scottish Medicines Consortium	http://www.scottishmedicines.org.uk
SMR	Service Medical Rendu (clinical added value)	
SSF	Belgian Special Solidarity Funds (Bijzonder Solidariteitsfonds / Fonds Spécial de Solidarité)	http://www.NIHDI.fgov.be/care/nl/info/solidarity/index.htm
WGO	Stuurgroep Weesgeneesmiddelen (Dutch Steering Committee on Orphan Drugs)	www.weesgeneesmiddelen.nl
WHO	World Health Organisation	www.who.org
ZonMw	Dutch Organisation for Health Research and Development	http://www.zonmw.nl/

I INTRODUCTION

An rare disease is generally defined as a disease with a very low prevalence. Different operational definitions for rare diseases are used in legal documents and in literature. As such, the definition used in Europe differs from the one used in the United States.

Rare diseases are often difficult to diagnose and specialized clinicians are most often scarce. Moreover, (drug) treatments for rare diseases are less likely to be produced by private companies because the market is too small and research and development costs for orphan products are usually too high to make the products profitable. Drugs used for the treatment of a rare disease are hereafter called orphan drugs.

Both in the US and in the European Union incentives have been created to promote research and development on orphan drugs. Between 2000 and 2008 more than 590 medicinal products received European orphan drug status. Almost 50 received marketing Authorisation in this period. About 30% of these were in the field of oncology and 27% in the field of endocrinology and metabolic disorders.

It is estimated that there are currently between 5 000 and 8 000 different diseases that can be classified as rare. With less than 50 orphan drugs on the market at the end of 2008, only a small part of the need for treatment of rare diseases is covered.

Given the increasing number of orphan drugs and the high costs of orphan drugs, budgets spent to orphan drugs continue to increase. While in absolute numbers the total budget impact of orphan drugs might still be limited (about 2% of total hospital drug expenditures in 2009), their relative budget impact becomes steadily more important.

As reimbursement policies with respect to orphan drugs differ between countries, access to orphan drugs also differs between countries. In the Belgian context, reimbursement of a product in Class I^a requires evidence of the added therapeutic value of the product. However, due to the small number of patients with an rare disease, the clinical evidence base will often be weaker for orphan drug than for regular drugs. Economic evaluations of orphan drugs are often hampered by the limited evidence on clinical effectiveness for the drug. Moreover, using traditional approaches economic evaluations will usually find that orphan Drugs are not cost-effective because the cost for the additional health benefit the orphan drug treatment offers is usually high compared to many non)orphan treatments.²

The specific features of rare diseases and orphan drugs combined with the increasing number of rare diseases, makes them an issue of high priority for policy makers. On the one hand policy makers are faced with an increasing proportion of the health care budget being spent on orphan drugs, on the other hand they have to recognize the ethical and social dimension of rare disease treatment and deal with these under the constraint of not being able to expect the same level of clinical evidence for orphan drugs as for other drugs.

^a There are three added value classes in Belgium – the therapeutic value of a medicinal product is decided by the DRC and expressed in an added value class
Class 1: medicinal products of which the therapeutic added value has been proven compared to existing therapeutic alternatives
Class 2: medicinal products with no proven therapeutic added value compared to existing therapeutic alternatives
Class 3: other medicinal products – categorized according to legislation
Source: art. 5 Royal Decree 21/12/2001

I.1 OBJECTIVES OF THIS STUDY

The main objectives of this study are:

1. to provide an overview of the commonly used definitions for 'rare diseases' and 'orphan drugs' and describe the particularities of orphan drugs compared to regular drugs;
2. to describe the regulatory process followed by an orphan drug, from orphan designation at the European level to reimbursement in Belgium and examine to what extent the information produced by the authorities responsible for orphan designation and Marketing Authorisation is directly useful for the drug reimbursement decision process;
3. to compare the Belgian policy with regard to the reimbursement of orphan drugs with the procedures that exist in other countries for decision-making about the reimbursement of orphan drugs;
4. to estimate the current budget impact of orphan drugs and make a prudent forecast of the expected budget impact in the years to come, and
5. to formulate recommendations for policy makers concerning orphan drugs.

Chapter 2 gives an overview of the different definitions for rare diseases and orphan drugs. Chapter 3 describes the European process from orphan designation to Marketing Authorisation and compares this with the process in the US. Chapter 4 compares the orphan drug reimbursement policies of 6 countries, including Belgium. Chapter 5 describes the extent to which the information provided by the pharmaceutical companies to EMEA in order to obtain Marketing Authorisation and the public assessment report produced by EMEA corresponds with the information available to the Belgian drug reimbursement committee (DRC) at the time drug reimbursement is requested. Chapter 6 includes an analysis of the current budget impact of orphan drugs in Belgium and makes a prudent forecast of the expected budget impact in the coming years. Chapter 7 contains a discussion of the issues related to orphan drugs and chapter 8 concludes the report with a number of recommendations for European and Belgian policy makers. We recommend to readers who want a quick insight to read the executive summary and chapter 7.

I.2 GENERAL METHODOLOGY OF THE STUDY

The methodology followed for this project can be summarised into seven activities.

Activity 1: Desk research

As a first activity, the contextual situation of the policy with regard to rare diseases and orphan drugs in Belgium was analysed against the European background. This included a collection and review of relevant documents and scholarly publications relating to the particularities of orphan drugs (such as market access, pricing, patient care, health technology assessments ...).

Activity 2: Policy description of the processes at EMEA and FDA

The aim was to compare the Orphan Designation and Marketing Authorisation processes of the EMEA and FDA. Information was collected through desk research and interviews.

Activity 3: Comparative analysis of the Belgian situation and of five other EU countries

The third activity focussed on the Belgian reimbursement procedure: a description is provided of the criteria used for reimbursement of orphan drugs and of the differences of the decision process compared to other medicinal products. This work is based on qualitative research and interviews. The description of the Belgian situation is followed by an overview of the reimbursement procedure in France, Italy, the Netherlands, Sweden and the United Kingdom. Information for this activity was collected through desk research and a survey based on a qualitative questionnaire.

Activity 4: Budget impact analysis

For all reimbursed orphan drugs in Belgium the budget impact was estimated based on the budget impact analysis presented by the companies in reimbursement request files and publicly available information (analysis of actual and expected budget impact over the years). Also forecasts and simulations of expected future budget impact of orphan drugs were made, using as a basis the average number of drugs getting marketing authorisation each year, the percentage of orphan drugs obtaining reimbursement in Belgium and the average cost per patient per year of orphan drugs.

Activity 5: Critical assessment

The critical assessment consisted of a 'quick scan' for all reimbursed orphan drugs in Belgium and a more in depth critical appraisal of eight cases (eight reimbursed and one negative case). The quick scan looked at the clinical and economic evidence provided in the context of the registration and reimbursement request files submitted to the NIHDl, whereas the in depth critical appraisal took into account the methodological standards of registration and reimbursement request files. The eight cases were selected according to a number of selection criteria (defined by the experts).

Activity 6: Discussion of issues

In Chapter 7 of this report eleven "issues" are presented which were identified through the study and which deserve attention at the policy-making level. This discussion offers some considerations which may serve as input for recommendations that follow from this study.

In addition, personal interviews complemented the various other techniques used for the activities described above. These interviews took place with key actors involved in the process, both at the national and at the EU level, as well as with representatives of the various stakeholders, from COMP members, over EMEA or NIHDl to patient organisations and the pharmaceutical industry.

Activity 7: Recommendations

The recommendations were written by the KCE based on the results of the scientific review.

Important comment for the reader: most figures mentioned in this report in relation to the number of orphan drugs are based on the situation as of the 31st of December 2008.

2 ORPHAN, RARE AND NEGLECTED DISEASES AND DRUGS: DEFINITIONS AND PARTICULARITIES

2.1 INTRODUCTION

Some conceptual confusion exists around the terms 'rare diseases' and 'orphan drugs'. Different definitions of rare diseases and of orphan drugs are used in existing legislation of various countries and in literature on the subject. This chapter gives an overview of commonly used definitions. Orphan drugs are distinct from common drugs in terms of their development, Marketing Authorisation (MA), pricing, reimbursement and post-marketing follow-up. This chapter also discusses economic challenges of developing and marketing orphan drugs.

2.2 METHODOLOGY

A review of the international literature was carried out by searching the following electronic databases up to November 2008: PubMed, EMBASE, Bath Information and Data Services, Cochrane Library, EconLit, and Social Science and Citation Index. Search terms included 'orphan diseases', 'rare diseases', 'neglected diseases', 'orphan drugs', 'ultra-orphan drugs', 'research and development', 'Marketing Authorisation', 'pricing', 'reimbursement', 'health technology assessment', 'economic evaluation', 'cost-effectiveness', 'post-marketing follow-up', 'risk sharing', 'patient registry', 'access' and 'equity'. Additionally, the bibliography of included studies was checked for other relevant studies. Finally, information about regulation with respect to rare diseases and orphan drugs was gained from documents setting out international/national legislation.

2.3 ORPHAN, RARE AND NEGLECTED DISEASES AND DRUGS

The terms 'orphan disease' and 'rare disease' are frequently used interchangeably for a disease that affects only few persons in the population. However, according to some definitions orphan diseases comprise rare diseases as well as 'neglected diseases'³. The latter group consists of conditions that are prevalent in developing countries which are too poor to pay drug prices that render the new drug profitable for the patent-holding manufacturer.⁴ This study will only focus on the group of rare diseases.

When is a disease rare? The definitions that are used vary, but are usually expressed in prevalence figures. Table 1 gives an overview of the number of patients per 100 000 individuals that countries apply to define a rare disease.

According to the definition put forward by the European Union (EU), rare diseases are life-threatening or chronically debilitating conditions with a prevalence of 50 out of 100,000 or less⁵. According to the World Health Organisation, a rare disease affects at most 65 out of every 100,000 individuals.³ Australia, Japan and the United States have set prevalences of 11⁶, 40⁷ and 66⁸ per 100,000 individuals respectively for a given rare disease. The Swedish National Board of Health and Welfare defines rare diseases as disorders or injuries that result in extensive handicaps and that affect no more than 10 per 100,000 individuals.⁹

Table 1: Definitions of rare diseases based on prevalence

Country	Rare diseases Prevalence on 100,000	Source
US	66 ^a	Orphan Drug Act 1983
EU	50	Regulation EC n° 141/2000
Japan	40	Orphan Drug Act 1993
Australia	11	Orphan Drug Program 1997
SE	10	Swedish National Board of Health and Welfare
FR	50	Regulation EC n° 141/2000
NL	50	Regulation EC n° 141/2000
WHO	65	WHO

^a Based on a total US population of 304,354,998 on 16 June 2008. Source: US Census Bureau (<http://www.census.gov/>). In scholarly literature, the US prevalence rates for Orphan Designation expressed per 10,000 inhabitants vary from less than 6 to 'about 10' though.

Within the group of rare diseases, some diseases are relatively more common than others. As a result, a distinction is sometimes made between rare diseases and ultra-rare diseases. Ultra-rare diseases are generally defined as affecting less than 10,000 individuals on a population of 300 million individuals.¹⁰ In the UK, the National Institute for Health and Clinical Excellence (NICE) sets the prevalence of an ultra-rare disease at less than 2 per 100,000 individuals.¹¹

Regardless of the country-specific definition, it is estimated that between 5,000 and 8,000 distinct rare diseases exist today, 80% of which have identified genetic origins. Other rare diseases are the result of bacterial or viral infections and allergies, or are due to degenerative and proliferative causes. Together, rare diseases affect an important part of the population, estimated to be about 6% - 8% of the population of the European Union (EU), equivalent to 27-36 million people.¹²

2.4 ORPHAN DRUGS

2.4.1 Background

Due to their relatively low prevalence, rare diseases as a whole have traditionally been neglected by large parts of the scientific, medical and political communities.¹³ With knowledge and awareness of the majority of rare diseases being scant or even absent, delay in diagnoses, lack of relevant information and difficulty in finding specialised physicians are common problems for affected patients. While many patients even remain completely undiagnosed, even when recognised, thousands of rare diseases cannot be treated because no therapies or drugs exist for them. This is primarily due to the fact that pharmaceutical companies are more interested in developing drugs for common disorders that affect millions of people than in the treatments for a few^{14 2005} and because of a scientific deficit as research is less oriented towards rare diseases. As a consequence, sufferers from rare diseases are not only disadvantaged in terms of likeliness and timeliness of being diagnosed as such, but are on top of that experiencing unequal access to therapy and treatment in comparison to patients suffering from 'common' diseases.¹⁵ In the past decades, this unequitable situation gained recognition as a serious public health problem and it became clear that the development of drugs for rare diseases required special encouragement.

2.4.2 Definitions

Orphan drugs are considered differently from other types of drugs by regulatory authorities. At EU level, discussions on orphan drugs started in the late nineties and led to the adoption of Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999, in which the justification for treating orphan drugs differently has been formulated as follows (preamble, paragraphs 1 and 2):⁵

1. (Whereas...) some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions; these medicinal products are called 'orphan';
2. (Whereas...) patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry;

Defining an 'orphan drug', Regulation (EC) No 141/2000⁵ states (in Article 3.1) that:

A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand persons in the Community when the application is made, or

That it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;

and

(b) that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

In summary, the arguments put forward for considering orphan drugs differently than other drugs in the EU lie in the orphan drugs being **economically not viable** under normal market conditions and considerations of **patient equity**.

2.4.3 Development

In the EU, companies with an Orphan Designation for a medicinal product benefit from incentives such as:¹⁶

- protocol assistance (scientific advice during the product development phase);
- direct access to the European Medicines Evaluation Agency (EMA) Centralised Procedure with respect to registration;
- Marketing Authorisation (10-year marketing exclusivity);
- financial incentives (fee reduction^b or exemptions, possible assistance with research and development)^c;
- national incentives (detailed in an inventory of incentives made available by the European Commission¹⁷).

^b Including a 100 % fee reduction for protocol assistance and 50% reduction for the application for Marketing Authorisation and 100% fee reduction for pre-authorisation inspections

^c In 2007, the funds made available by the Community for fee exemptions for orphan medicinal products amounted to € 6,000,000 (EMA, 2007).

Article 9 of Regulation (EC) No 141/2000 requires Member States to communicate to the Commission detailed information concerning any measure they have enacted to support research into, and the development and availability of, orphan medicinal products or medicinal products that may be designated as such. The European Commission regularly publishes an inventory of such measures taken by the Member States according to article 9.^d

In the United States, incentives for the development of orphan medicinal products have been available since 1983. The United States' Orphan Drug Act (ODA)⁸ provides significant incentives for sponsors to develop and bring to the market drugs and biologicals, including vaccines and *in vivo* diagnostics to tackle rare diseases¹³. These benefits include expedited review by the US Food and Drug Administration (FDA) and thus shorter approval time, tax credits, seven years of marketing exclusivity and reductions of certain fees. Marketing exclusivity means that similar products have no access to the market for seven years. Furthermore, research grants are available to support clinical trials of orphan drugs. To qualify for incentives, drugs must receive the 'Orphan Designation' from the FDA's Office of Orphan Products Development (OOPD), and then go through the normal evaluation process for safety and efficacy.¹⁸ The ODA specifies, next to the prevalence criterion, that a drug is also considered as an orphan drug if scientists and economists at the Food and Drug Administration (FDA) determine that it will not be profitable for seven years after FDA approval.

It should be noted that incentives for developing orphan drugs are important, but only constitute a means to an end.² The ultimate success of such incentives should be measured in terms of the increase in life expectancy and quality of life of patients with rare diseases.

Chapter 3 deals in more detail with the comparison between the policies of the FDA and EMEA.

2.4.4 Marketing Authorisation

Figure 2.1 presents data on the number of Orphan Designations and Marketing Authorisations for orphan drugs, issued by the FDA and the EMEA from 2001 until 2007.

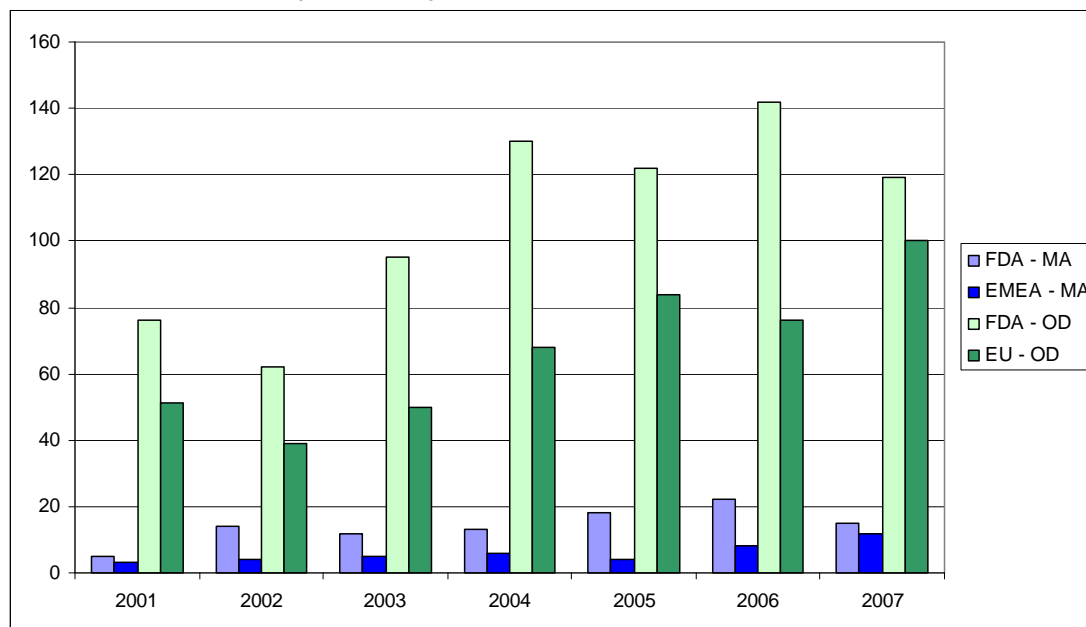
Since the EU developed a Regulation in 2000 to promote research and development on orphan drugs, about 270 medicinal products received European Orphan Designation and 22 received Marketing Authorisation from EMEA by 2005. These numbers increased to 570 with Orphan Designation and 47 that received MA by December 2008. In the USA, more than 240 orphan drugs reached the American market in the 20 years following the Orphan Drug Act became law, and over 900 experimental orphan drugs are in the research pipeline.¹⁹

The rapid increase in the number of Orphan Drug Designations and Marketing Authorisations give rise to general concerns regarding the budget impact these drugs have and will have on the existing health care systems and health care payers (both public and private) and the extent to which the current governance support to these drugs is economically sustainable^{2 14 18}.

Figure 2.1 gives an overview of the number of approved Orphan Designations and Marketing Authorisations by the FDA and the EMEA since 2001. The discrepancy between the numbers of FDA and EMEA is explained by the fact that the approvals in the USA started in 1984, increasing steadily over the years.

^d See inventories of 2001, 2002, 2005 ¹⁷

Figure 2.1 : Orphan Designation and Marketing Authorisation by the FDA and EMEA (2001-2007)



OD: Orphan Designation;
MA: Marketing Authorisation

2.4.5 Pricing

Prices of orphan drugs tend to be high. Both Genzyme and Shire, for example, are marketing some drugs in the EU with annual costs of € 200.000 to € 300.000 per patient (e.g. Aldurazyme® for mucopolysaccharidosis I and Fabrazyme® for Fabry disease).²⁰ There are several potential reasons for the high prices of orphan drugs. High prices may originate from marketing exclusivity, implying that no marketing authorization can be granted to a similar product with similar efficacy for the same therapeutic indication for a period of 10 years. The non-existence of an alternative treatment combined with the 10-year market exclusivity creates a monopoly for the company producing the orphan drug. It should be noted, however, that marketing authorization can be granted to a clinically superior product, even if it is a similar product and market exclusivity can be reduced to 6 years if the criteria for orphan designation are no longer met. Also, the substantial costs of research and development have to be recouped from a small number of patients, thus resulting in high drug acquisition costs per patient.¹³ However, orphan drugs do not always target a small number of patients.

Certain products that were originally approved as orphan drugs, and as such benefited from special measures, later became top sellers either because the once rare condition they were intended to treat increased in frequency or because they proved also effective against more common disorders.¹³ In these cases where profitability proves not to be a problem, public support is ex post deemed unjustified and critics in the US therefore urge for corrections to be made to the orphan drug legislation. In the EU, however, Article 8 of the Regulation provides for the possibility to reduce the marketing exclusivity to six years instead of ten years if, at the end of the fifth year, it is established that the product is sufficiently profitable.^f Unsurprisingly, pharmaceutical companies lobby strongly against this article being put into practice and even argue that it should be eliminated completely.²¹ Fact is also that there is no agreed definition of what is meant by “sufficiently profitable”.

^e Examples are Glivec® and Sutent®.

^f Situation on July 9th, 2009

2.4.6 Health technology assessment and reimbursement

In a context of spiralling health care costs and limited resources, public policy makers and health care payers are increasingly using health technology assessments, including economic evaluation and budget impact analysis, to inform reimbursement decisions. However, the use of health technology assessment in the field of orphan drugs for reimbursement purposes is challenging for a number of reasons as described below.

The **reimbursement** of orphan drugs is not regulated at EU level, but is a national responsibility of Member States. Once products have received Marketing Authorisation from EMEA, there are important differences to be noted among the EU Member States in terms of availability of these products on these markets, in the delays of availability between the Member States and in the prices of the same orphan medicine between the Member States.¹⁹ Based on these observations, patient groups like the European Organisation for Rare Diseases (Eurordis) and the European Genetic Alliance Network (EGAN) are arguing for the elimination of regional and national differences in distribution, taxation and reimbursement policies, factors which combined explain the differences of up to 70% for the annual cost per patient of a given orphan medicine between various EU countries.¹³

Given their high price for an often modest health benefit orphan drugs are unlikely to be cost-effective, at least if the cost-effectiveness of an intervention is judged based on its cost per quality adjusted life year (QALY) gained in its neo-classical welfarist sense, and this cost-per-QALY is compared to a fixed threshold value.²² If reimbursement decisions are primarily based on cost-effectiveness considerations and budget impact, orphan drugs will tend to fail these criteria. However, most often additional criteria that are not included in the traditional cost-per-QALY measure, are used to inform reimbursement decisions.²² For instance, the Pharmaceutical Benefits Advisory Committee of Australia also takes account of: the seriousness of the health condition; the availability of other therapies to treat the disease; and the cost to the patient if the drug is not reimbursed.²³ These criteria are particularly relevant to orphan drugs, which tend to target serious health conditions, make up the single strategy to treat a disease, and have a huge impact on patients' health care expenditures if they would have to pay for the drugs themselves.

With a view to assessing the effectiveness of an orphan drug, it is difficult to enrol a sufficient number of patients in clinical trials. As these diseases affect only few patients at a time, it is in many cases hardly possible to gather enough patients to achieve sufficient statistical power to demonstrate clinical effectiveness of a given treatment.²⁴ Moreover, also because the disorders are rare, few medical centres will have sufficient long-term experience with affected patients to be able to describe the natural history of the diseases. Other authors also point out that in many rare disorders there is a lack of knowledge on disease processes, on the precise influence of genetics, on prevalence figures, and on how to conduct clinical trials.¹⁹ These authors emphasise that increased efforts to address these issues are urgently needed at the European Community level.

One of the authors therefore suggests to modify the review process for rare disease therapies: allow greater use of rational surrogate outcome measures if clinical efficacy data are incomplete, but require from industry to support a process of continuing review of clinical outcomes. A central component of the process would therefore be a commitment to ongoing evaluation of patients through registries designed to collect clinical information on patients receiving the new therapy.²⁴

A patient registry would allow regulatory authorities to follow up and evaluate the uncertainties surrounding longer-term effectiveness and cost-effectiveness of an orphan drug in the relevant population.²⁵ Such an approach would support the decision-making process and allow more timely access to orphan drugs for patients. Also, data on (cost-) effectiveness from patient registries can be used by researchers and clinicians to inform clinical practice and prescribing guidelines. Such patient registries could even be integrated with national pharmacovigilance systems providing information about adverse events associated with orphan drugs. However, it should be noted that there are challenges involved in setting up a patient registry and analysing registry data. They could also be different if set-up independently or by industry.

The patient registry may be biased as the patient aetiology and disease severity change over time. Also, as patient registries collect data on an orphan drug, but not on alternative treatments, they only provide partial information to calculate the incremental cost-effectiveness of the orphan drug relative to an alternative treatment. Furthermore, new treatment strategies may become available during the period covered by the registry. Therefore, patient registries need to be set up and developed in a flexible way to be able to account for changes in patient population and treatment strategies over their lifetime.

For instance, the MPSI Registry is an ongoing, observational database that tracks natural history and outcomes of patients with MPSI⁸. Initiated worldwide in April 2003, data from over 718 patients with MPSI have been collected from physicians in over 30 countries as of May 2008.

Reimbursement may not only depend on the value for money of an orphan drug at the time of the reimbursement application, but also on its value after a number of years following the admission to the reimbursement system. Under such a system of conditional reimbursement, pharmaceutical companies need to explore setting up patient registries to inform the post-launch cost-effectiveness of an orphan drug.

Reimbursement authorities may also wish to consider a risk-sharing scheme between drug sponsor and government based on a registry system whereby survival outcomes are linked to future drug prices.²⁵ Risk-sharing agreements allow authorities to balance the uncertainty of long-term cost-effectiveness with the need to provide equitable access to potentially effective but expensive orphan drugs. Such agreements may incite the drug sponsor to promote responsible prescribing of orphan drugs; provide a guarantee on health outcomes with a view to attaining predictable health gains for a given drug expenditure; and share the budgetary risks between authorities and the drug sponsor. However, risk-sharing agreements entail that structures are set in place that safeguard the objective of computing the post-marketing cost-effectiveness of orphan drugs based on a representative and unbiased sample. Also, risk-sharing agreements should be flexible to reflect the introduction of new treatment strategies over the monitoring period of the agreement. Nevertheless, Owen et al. conclude that such schemes may allow to **balance the uncertainty of long-term cost-effectiveness with the public demand for equitable and timely access to new orphan drugs**, on the condition that some issues like governance, privacy, ethics review, timely and accurate data, related to such registry system are adequately addressed.²⁵

2.5 CONCLUSIONS

A wide variety of definitions of rare diseases and of orphan drugs are used in the legislation of various countries. Also, a number of challenges exist with respect to the development, Marketing Authorisation, pricing, reimbursement and post-marketing follow-up of orphan drugs. As a result, the need is expressed for more transnational cooperation and the building of an active and international community able to act and address the economic and intellectual efforts towards solving the most pressing difficulties as described above.¹⁹

⁸ <http://www.lsdregistry.net/mpsiregistry/>

Key points

- Different definitions of rare diseases and of orphan drugs are used in the existing legislation of various countries and in literature. For the purpose of the present study, EU official definitions for rare diseases and for orphan drugs are adopted.
- Rare diseases are life-threatening or chronically debilitating conditions with a prevalence of 50 out of 100 000 or less.
- Due to their relatively low prevalence, rare diseases have traditionally been neglected by large parts of the scientific, medical and political communities. As a result, patients suffering from rare diseases may experience unequal access to treatment in comparison to patients suffering from 'common' diseases.
- In the EU, orphan drugs are considered differently from other drugs for reasons of absence of economical viability under normal market conditions and because of considerations of patient equity. With a view to supporting the development of orphan drugs, the EU has put in place a number of incentives.
- However, the resulting rapid increase in the number of orphan drugs obtaining designations has given rise to concerns about the overall potential budget impacts on health care systems and health care payers.
- Reimbursement decisions for pharmaceutical products are also based on cost-effectiveness considerations, but orphan drugs will tend to fail these criteria because the cost of orphan drug treatments is usually high for the benefits they offer compared to many non-rare disease treatments. Additional criteria, such as the seriousness of the disease and the availability of other therapies, can become more important in reimbursement decisions of orphan drugs but are generally not incorporated in a standard economic evaluation.

3 POLICY DESCRIPTION

3.1 INTRODUCTION

The process from Orphan Designation to Marketing Authorisation is governed by the European Medicines Agency (EMA) in Europe and the Food and Drug Administration (FDA) in the United States. This chapter compares the EMA and FDA procedures with a view to identifying differences and discussing the implications of different approaches to Orphan Designation and Marketing Authorisation.

3.2 EMA PROCESS: FROM ORPHAN DESIGNATION TO MARKETING AUTHORISATION

3.2.1 Presentation of EMA

*“The European Medicines Agency is a decentralised body of the European Union with headquarters in London. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use”.*²⁶

Until recently, the possibility also existed to obtain a Marketing Authorisation by a mutual recognition procedure. Since 2005, only the central procedure at EMA can be used to register a product and obtain Marketing Authorisation.

The two main actors in the orphan drug procedures are the Committee for Orphan Medicinal Products (COMP) and the Committee for Human Medicinal Products (CHMP).

The COMP is EMA's committee responsible for examining the applications for Orphan Designation: the European Commission (EC) will approve or reject an application based on the COMP's opinion. The COMP has two main activities:

Scientific evaluation	Public Health Activities
<ul style="list-style-type: none"> • To examine applications for Orphan Drug Designations • Protocol assistance • Re-evaluation of significant benefit during Marketing Authorisation registration • Post-Marketing Authorisation review every 5 years 	<ul style="list-style-type: none"> • Advise the EC on the establishment and development of a policy on orphan medicinal products for the EU • Assist the EC in liaising internationally on matters relating to orphan medicinal products, and in liaising with patient support groups • Assist the EC in drawing up detailed guidelines • EU expert network and visibility

The COMP is composed of:

- one chairperson and one vice-chairperson;
- one member per Member State (27 Member States in 2008);
- three members representing patient organisations (nominated by the EC);
- three members recommended by EMA (nominated by the EC);
- one non-voting member per EEA-EFTA^h state (Norway and Iceland in 2008).

The members are appointed by their country, while the chairperson and vice-chairperson are elected by and from the COMP members on basis of a brief resume of the candidates and with an absolute majorityⁱ.

^h EEA-EFTA: European Economic Area – European Free Trade Association

ⁱ An absolute majority is obtained when more than 50% of the members has voted in favour of the candidate.

All the members are appointed for a period of three years with possibility of renewal (the same applies for the CHMP members).

The CHMP is the committee responsible for examining the applications for Marketing Authorisation for all medicinal products, but also for the post-authorisation follow-up.

The CHMP is composed of:

- a chairman, elected by and from the CHMP members;
- one member (and an alternate) per Member State (27 Member States in 2008);
- one member (and an alternate) per EEA-EFTA state (Norway and Iceland in 2008);
- up to five co-opted members (experts recruited to gain additional expertise in a particular scientific area).

The European Orphan Drug policy has been regulated by Regulation (EC) No 141/2000⁵ on orphan medicinal products. There are two steps to be taken before an orphan drug is admitted on the market:

- Step 1: Orphan Designation: a medicinal product receives the orphan status – linked to incentives.
- Step 2: Marketing Authorisation: is the marketing approval of a drug for an orphan condition. It becomes orphan drug and receives market exclusivity.

3.2.2 Applying for Orphan Designation

3.2.2.1 *Conditions to be fulfilled*

A medicinal product can obtain the designation of orphan medicinal product if it provides treatment for a rare disease. In order for a pharmaceutical firm to be able to apply for an Orphan Designation, two conditions must be fulfilled (see art. 3 of Regulation (EC) no 141/2000):

- the medicinal product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition that either affects less than 5 in 10,000 persons of the Community; or that without incentives it is unlikely that the marketing of the medicinal product would generate sufficient return to justify the expenditure;
- a satisfactory method for diagnosis, prevention or treatment of the condition does not exist.

The COMP will essentially take decisions at two levels corresponding to the two conditions defined in the above-mentioned article of the Regulation:

Level 1: **Prevalence** or **Insufficient return**

Level 2: **Absence of solution** or **Significant benefit**

Other criteria to obtain Orphan Designation are: the “medical plausibility” of the condition and sub-setting.

In case of **insufficient return** it is unlikely that the expected return would justify the required investment and so it is unlikely that the sponsor would be prepared to make the investment.²⁷

Absence of solution means that there is no alternative treatment available, while **significant benefit**²⁸ means that the drug has a clinically relevant advantage or major contribution to patient care compared to existing satisfactory methods for diagnosis, prevention or treatment. The significant benefit can be related to:

- improved efficacy and / or safety;
- ease of self administration: leading to a major contributions to patient care;

- new mechanism of action: of which the efficacy will have to be demonstrated. This new mechanism opens possibilities for drug combination and can be designated as a therapeutic alternative²⁹;
- reduced availability of the base materials;
- reduced availability of the product in the EU Member States (not possible after centralised registration).

Significant benefit must be confirmed by the sponsors during registration application, and questions about it must have been answered during protocol assistance. Appraisal of the criterion thus occurs at three times: 1. first application at COMP for Orphan Designation; 2. protocol assistance prior to Marketing Authorisation; 3. MA registration application (compulsory). The COMP will assess if the significant benefit can be confirmed by available data and/or evidence supplied by the applicant (at the moment the CHMP takes its decision).

A **subset**²⁸ is a separated part of a (frequently occurring) disease, having an own pharmacotherapeutic treatment and without this subset the drug would have no effect in the remaining population. Sub-setting is rarely accepted. Are not accepted:

- different levels of seriousness or localisation of a disease;
- the subset is based on a (post-hoc) analysis of the study of a product that should function for the whole group.

Sub-setting can lead to so-called “salami-slicing”: this is creating artificial subsets of a non-orphan condition, by basing the prevalence criterion on an unreal subpopulation. The aim is to obtain market exclusivity, a decrease of the costs and obligations linked to the registration demand, and an increase of the exclusivity through new subpopulations (also known as the “evergreening tactic”).

Medically plausible subsets are based on the real disease process; the seriousness of the condition; the characteristics of the drug; the working mechanism and the unique characteristics of the patient population. In order for a subset to be accepted, the sponsor must justify the medical plausibility why the drug should be restricted to the sub-set.³⁰

In practice, of the 541 molecules or products that received the designation, 540 obtained it based on the criterion “prevalence”, and one product obtained designation based on the criterion of “return on investment”ⁱ (a second application was withdrawn by the sponsor³⁰).

3.2.2.2 Orphan Designation Procedure

The application dossier must include:

- the name or corporate name and permanent address of the sponsor;
- active ingredients of the medicinal product;
- proposed therapeutic indication;
- a justification that the two conditions mentioned in article 3 are met;
- and a description of the stage of development, including the therapeutic indications expected.

The Orphan Designation procedure is described in figure 3.1. This is the centralised procedure which is compulsory for orphan drugs since 2005.^k

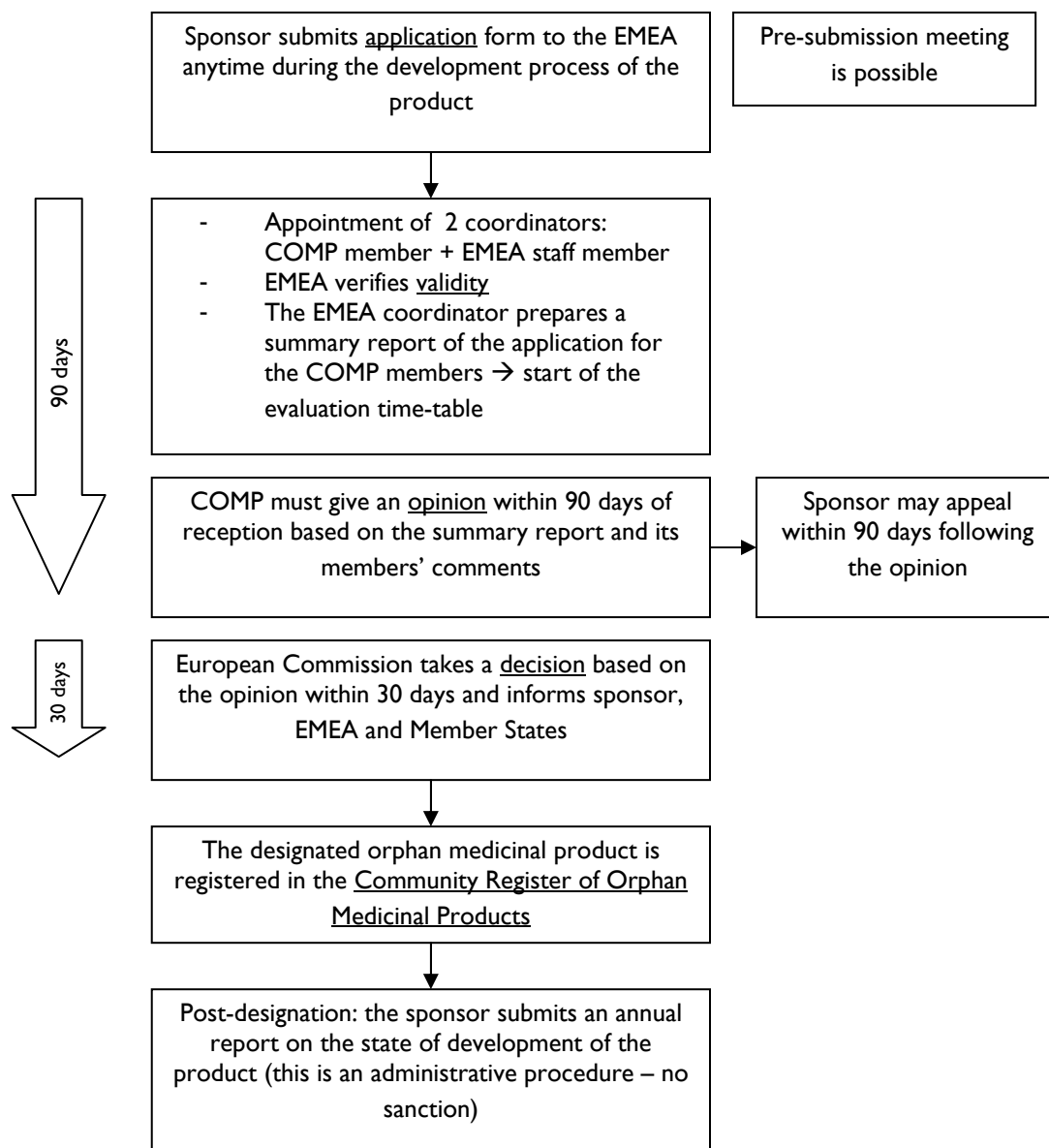
The COMP will adopt its opinion with a consensus, and if impossible with a two-thirds majority. The European Commission may take a draft decision that is different of the COMP’s opinion, but this decision must be approved by the Council of the EU (See art. 73 of Regulation (EC) 2309/93)³¹.

j This orphan drug designation was obtained for the treatment of neglected disease (as opposed to rare disease).

k For non-orphan drugs, it is also possible to proceed through the mutual recognition procedure and the decentralised or national procedure.

Following the publication of the orphan product in the Community Register of Orphan Medicinal Products, the sponsor will annually submit to the EMEA a report on the state of development of the product (See art. 5§10 of Regulation (EC) 141/2000)⁵.

Figure 3.1 : Orphan Designation Procedure



In order to encourage research and development of orphan medicinal products, the Orphan Regulation incorporates **five incentives**. The first incentive can take place before or after applying for Orphan Designation: thanks to the protocol assistance (1), the company may request scientific advice of the EMEA on the conduct of various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product. Once the medicinal product has been given the status of orphan, it has direct access to the centralised procedure (2) for the application for Marketing Authorisation. If this latter is granted, the orphan medicinal product receives a 10-year market exclusivity (3) meaning that similar products have no access to the market (unless they have a significant benefit or are superior).

Orphan medicinal products will also benefit from fee reductions (4) for centralised applications and obtain grants within the framework of EU-funded research (5) as well as priority access to EU research programs.

The market exclusivity can be brought back to six years if the sponsor having applied first for a designation gives its consent that a second sponsor can obtain the same designation; there is a lack of drug supply; or if the new drug is safer, more effective or clinically superior.²⁹ The market exclusivity may also be withdrawn after six years if the medicinal product no longer meets the two conditions necessary to obtain Orphan Drug Designation.

In 2007, 4.89 million € of fee reductions was granted through the fee reduction mechanisms (applicable after Orphan Drug Designation is obtained).

Figure 3.2 : Overview of incentives and other compensations

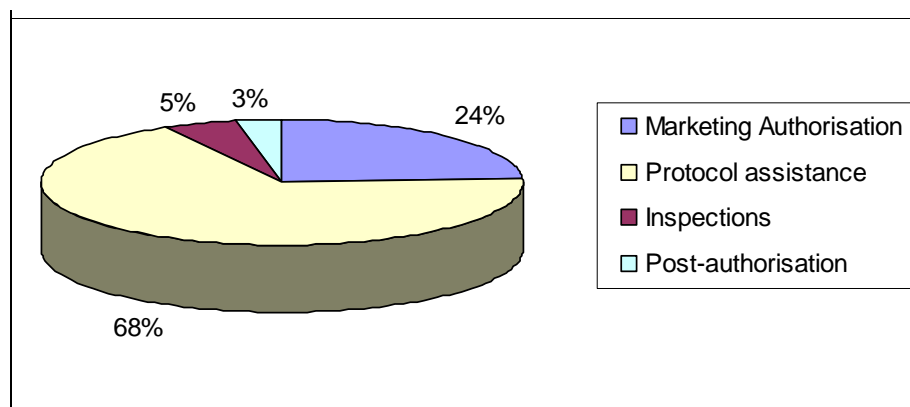
Incentives:

1. 10 years market exclusivity
2. Protocol and scientific assistance
3. Financial incentives on a national basis
4. Direct access to centralised procedure
5. Access to EU-funded research

Other compensations:

1. The fee reductions can be the following:¹⁶
 - 100% reduction for protocol assistance and follow-up;
 - 100% reduction for pre-authorisation inspections;
 - 50% reduction for applications for Marketing Authorisation;
 - 50% reduction for post-authorisation activities, including annual fees, in the first year after granting of a Marketing Authorisation.
2. 12-year market exclusivity if paediatric orphan drug (Paediatric development since 1/7/2008)
3. Guidance for clinical trials in small populations³² in order to increase the efficiency of the design and the analysis

Figure 3.3 : Use of EU special funding contribution for orphan medicines (2007)



Source: EMEA. Annual report of the European Medicines Agency 2007. Doc. ref.: EMEA/MB/17464/2008 13 May 2008. Available from <<http://www.emea.europa.eu/pdfs/general/direct/emeaar/AnnualReport2007.pdf>> [Last accessed: 10/12/2008].

The table in figure 3.4 gives an overview of the yearly number of applications for Orphan Designation since 2000. Of 896 initial applications 226 have been withdrawn. 92% of the remaining applications have received a positive COMP opinion and 89% a final designation.

Figure 3.4 : Orphan Designation between 2000 and November 2008

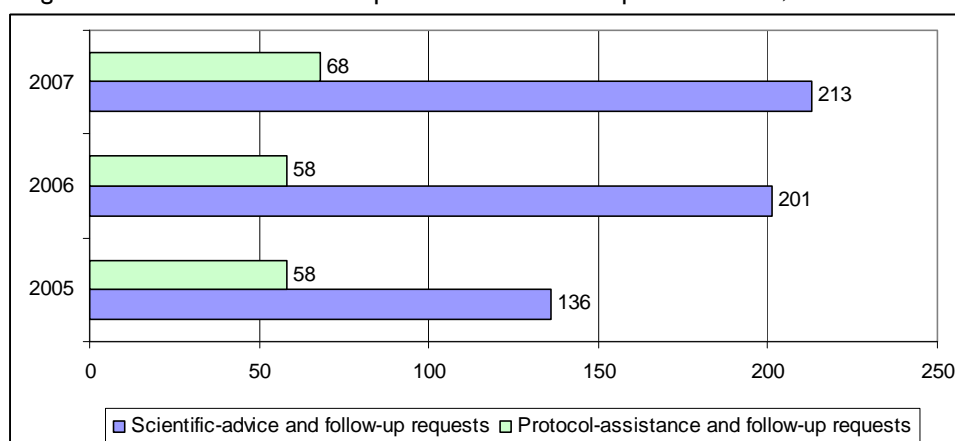
Year	Applications submitted	Positive COMP Opinions	Applications withdrawn	Final negative COMP Opinions	Designations granted by the Commission
2008	119	86	31	1	73
2007	125	97	19	1	98
2006	104	81	20	2	80
2005	118	88	30	0	88
2004	108	75	22	4	72
2003	87	54	41	1	55
2002	80	43	30	3	49
2001	83	64	27	1	64
2000	72	26	6	0	14
Total	896	614	226	13	593

Source: Committee for Orphan Medicinal Products. January 2009 Plenary Meeting, Monthly Report. EMEA. Doc. Ref.: EMEA/COMP/694107/2008. 7 January 2009. Available from <<http://www.emea.europa.eu/pdfs/human/comp/pr/69410709en.pdf>> [Last accessed: 10/3/2009].

3.2.3 Applying for Marketing Authorisation

Before applying for a Marketing Authorisation, the pharmaceutical company can request scientific advice and protocol assistance from the Scientific Advice Working Party (SAWP), part of the CHMP. The advice is given for the conduct of tests and trials in order to demonstrate the quality, safety and efficacy of the medicinal product (Art. 6 Regulation (EC) No. 141/2000)⁵, while the assistance provides guidance and verifies the criteria.

Figure 3.5 : Scientific-advice and protocol-assistance requests received, 2005-2007



Source: EMEA. Annual report of the European Medicines Agency 2007. Doc. ref.: EMEA/MB/17464/2008 13 May 2008. Available from <<http://www.emea.europa.eu/pdfs/general/direct/emeaar/AnnualReport2007.pdf>> [Last accessed: 10/12/2008].

The SAWP's tasks are to:³³

- provide the CHMP an integrated view about the quality, pre-clinical and clinical safety including pharmacovigilance and risk/minimisation aspects, and efficacy, relating to the development of orphan medicinal products;
- provide protocol assistance to the CHMP as regards the demonstration of significant benefit relating to orphan medicinal products;
- provide advice on applying for a conditional MA or MA under exceptional circumstances;
- provide advice on the design of trials to assess safety and efficacy in a new indication expected to bring significant clinical benefit compared to existing therapies;
- pay special attention to development and methodology issues of products intended for small populations.

In 2006, the CHMP developed guidelines on clinical trials in small populations. | They came into effect on February 1st, 2007. The guidelines acknowledge that in circumstances where only few patients are affected by a disease, a trial enrolling several hundred patients may not be practical or possible. Meanwhile it is stated that “most orphan drugs and paediatric indications submitted for regulatory approval are based on randomised controlled trials that follow generally accepted rules and guidance.” The guidelines state that “deviation from such standards is, therefore, uncommon and should only be considered when completely unavoidable and would need to be justified.”

After having received the Orphan Designation the sponsor can apply for a Marketing Authorisation (the procedure is presented in figure 3.6). This can only be done through the centralised procedure at the EMEA. For normal drugs, a national procedure exists as well. Within 210 days the CHMP gives a final opinion that is transmitted to the European Commission who will take the concluding decision.

The MA procedure consists of three steps:

1. Pre-submission
2. Primary evaluation
3. Secondary evaluation

An accelerated review of the medicinal product is possible when decided by the CHMP. The product must fulfil three conditions:

- the condition is life threatening or serious;
- there is no effective therapeutic alternative;
- and the drug is expected to have a high therapeutic benefit.³⁴

I. Pre-submission phase

The sponsor (named hereafter ‘applicant’) sends a letter of intent to the CHMP together with a fee for the examination. The CHMP examines the validity of the application:

- examination of the submitted particulars and documents;
- it may request that the medicinal product be tested;
- and it may request that the applicant supplements the particulars accompanying the application within a specific time period.

A rapporteur and a co-rapporteur will be appointed to evaluate the MA application. The appointment is based on the best available expertise. Each rapporteur will have an assessment team composed of assessors of the national authorities and can appoint experts if necessary.

¹ CHMP/EWP/83561/2005

Within EMEA, a product team leader and his/her team are appointed in order to prepare the documents of the CHMP and to liaise between the applicant and the CHMP.

2. Primary evaluation

On Day 80 of the MA process, the two rapporteurs each produce an assessment report in which is given a detailed overview of the quality, clinical and non-clinical data given in the submission file, and possibly a proposal of list of questions.

The assessment reports are sent to the CHMP members for comments and to the applicant for information. The reports are also peer reviewed by a CHMP member and by the EMEA product team leader in order to see if they are consistent and if there is a sufficient level of detail.

A list of questions is produced by the CHMP and sent to the applicant on Day 120.

3. Secondary evaluation

A Joint Assessment Report is produced by the rapporteurs following the reception of the responses of the applicant. The report is sent to the CHMP on Day 150 for comments resulting in a list of outstanding issues to be sent to the applicant on Day 180. Following the reception of the applicant's responses, a second joint assessment report is sent to the CHMP members.

The different assessment reports and the lists of questions serve as a basis for the redaction of the CHMP assessment report which underpins the CHMP opinion. The CHMP opinion is based on the examination of the risk-benefit balance of the medicinal product; this is an evaluation of the positive therapeutic effects of the medicinal product in relation to the following risks:

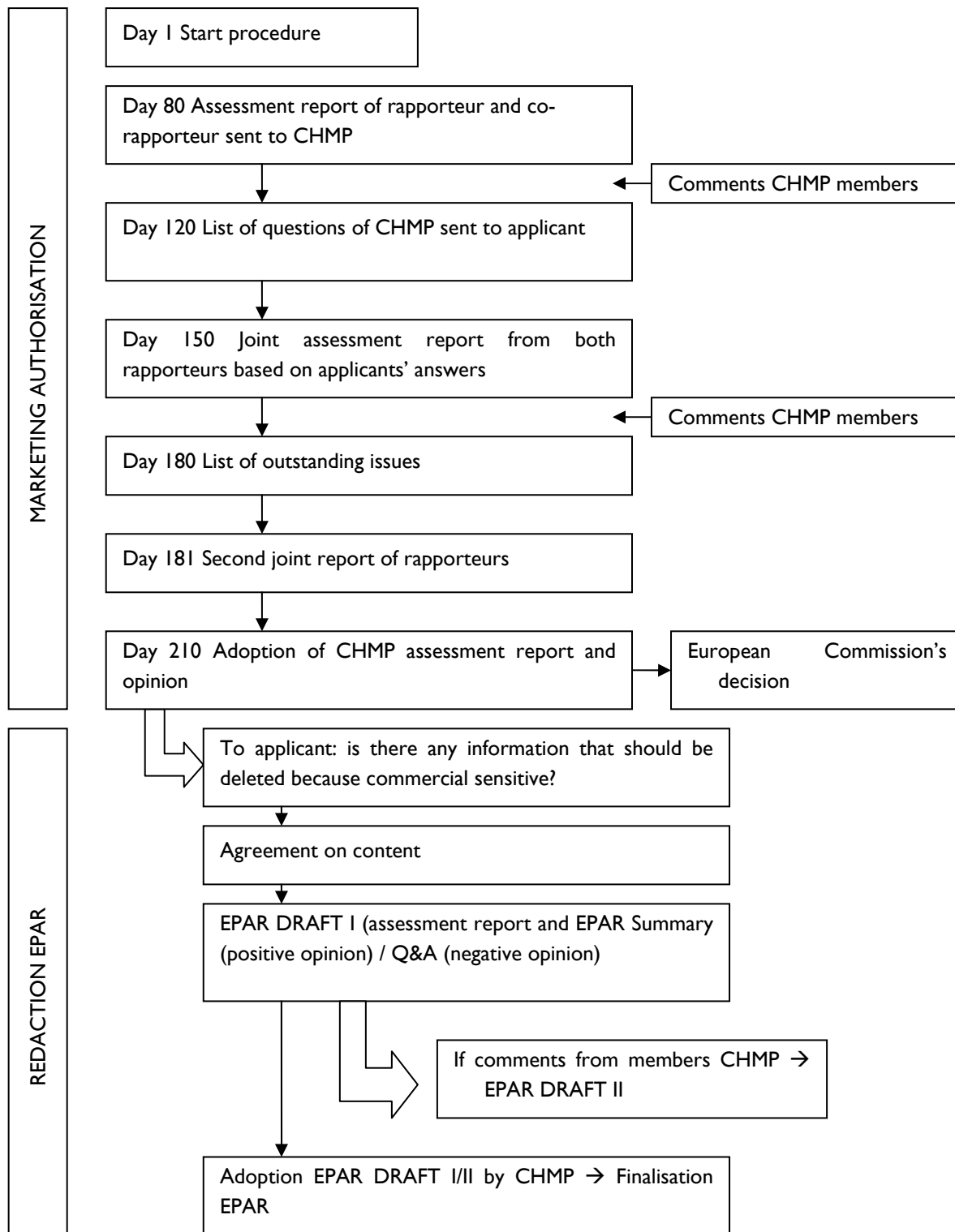
- any risk related to the quality, safety or efficacy of the medicinal product as regards patients' health or public health;
- any risk of undesirable effects on the environment.

The CHMP issues a positive or negative opinion based on the risk-benefit ratio. There is no comparison with other drugs.

The opinion is sent to the European Commission who takes the final decision. Refusal reasons are either that the quality, safety or efficacy of the product is not demonstrated; or that particulars or documents are incorrect. If the EC decision is different from the CHMP's opinion, then it will be sent to the Member States. The applicant is notified in both cases.

The CHMP assessment report also serves as a basis for the redaction of the European Public Assessment Report (EPAR) which is published on EMEA's website and available for the public.

Figure 3.6 : Marketing Authorisation Procedure



The MA procedure is the same for all human medicinal products, orphan and non-orphan drugs: EMEA evaluates the quality, safety and efficacy of the drug. The only differences for orphan drugs are:

1. the involvement of the COMP who will review the significant benefit criterion: are the criteria on which the decision for the Orphan Designation were taken still valid? This takes place when the CHMP prepares its opinion.
2. the existence of guidelines for clinical trials in small populations, which are used as a basis to assess the clinical evidence provided.

The MA is granted if:

1. The medicinal product contains a new active substance which was not authorised in the Community; **or**
2. The applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorisation is in the interests of patients at Community Level.

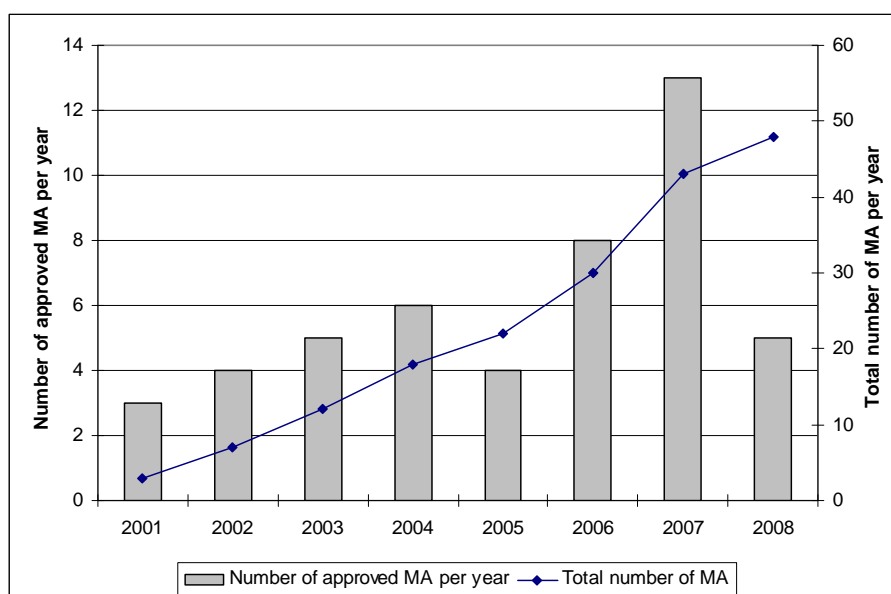
A medicinal product cannot receive a MA for an orphan indication **and** for a non-orphan indication. In case of conflict, the orphan indication will have to be disposed of or the medicinal product will have to request MA under a different name. For example, the drugs Viagra® and Revatio® have the same composition, but the first is reimbursed for a non-orphan indication, the second for an orphan indication (Pulmonary Arterial Hypertension).

The MA is valid for five years and can be renewed for five-year periods after review (Art. 13 Regulation (EC) No. 2309/93).³¹

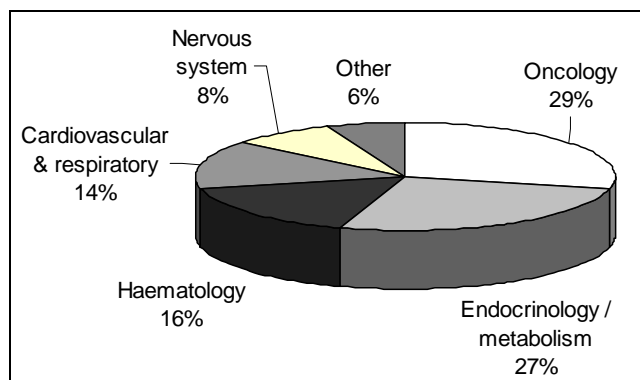
There is a possible access to accelerated review to MA if duly substantiated by the sponsor (150 days instead of 210 days). The review can be requested for medicinal products for human use which are of major interest from the point of view of public health and of therapeutic innovation.

In 2008, fourteen MA applications have been submitted for orphan medicinal products. Seven have received a positive opinion and two a negative opinion. Six sponsors have withdrawn their application prior to the opinion. The European Commission has granted five MA.³⁵

Figure 3.7 : Overview of Marketing Authorisations for Orphan Drugs (2001-2008)



Source: DG Enterprise EC. Register of designated Orphan Medicinal Products. <<http://ec.europa.eu/enterprise/pharmaceuticals/register/orphreg.htm>>. 11/3/2009.

Figure 3.8 : Total of Orphan Drugs per therapeutic area (December 2008)

Source: EMEA. List of orphan-designated authorised medicines 6/11/2008. Available from <<http://www.emea.europa.eu/pdfs/human/comp/56357508en.pdf>> [Last accessed: 7/5/2009].

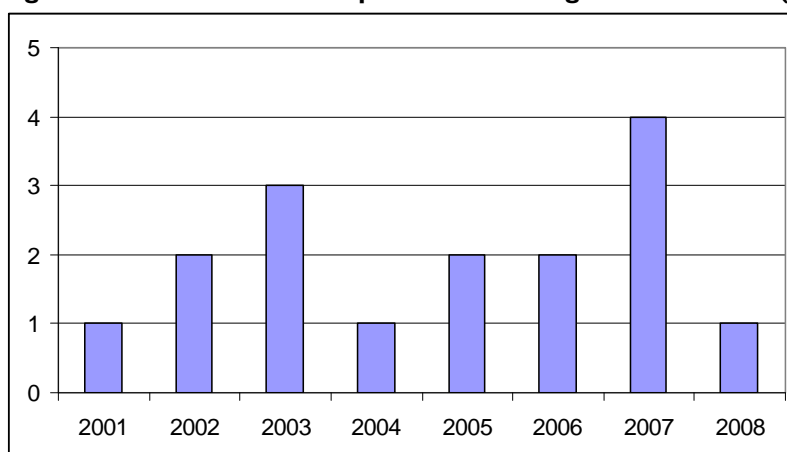
There are three types of MA: the normal MA, the conditional MA and the MA under exceptional circumstances.

The **normal MA** is valid for five years and may be renewed on the basis of a re-evaluation by EMEA of the risk-benefit balance. After this renewal, the MA will be valid for an unlimited period of time unless decided otherwise. The medicinal product must be placed on the market within three years otherwise the Authorisation is no longer valid. The same applies when the product has been unavailable for three consecutive years.

The **conditional MA** is regulated by Regulation (EC) 726/2004. This second type of MA is granted on the basis of less complete clinical data. Conditions are that the risk-benefit balance is positive, there is a benefit to public health of immediate market availability (outweighing the risks inherent to the fact that additional data are still required) and that unmet medical needs will be fulfilled. The conditional MA is valid for one year and can be renewed. Once the missing data have been completed, the drug will receive a normal MA.

The **MA under exceptional circumstances** is given when comprehensive data cannot be provided because of the small study population. This MA will be reviewed annually to reassess the risk-benefit balance based on follow-up studies including pharmacovigilance studies. The orphan drugs Tracleer® and Fabrazyme® have received normal MA after fulfilling the data.

As of December 2008, there was one orphan drug with a conditional MA and sixteen with an exceptional MA. This means that five out of eight orphan drugs are authorised under exceptional circumstances. Following figure shows that the exceptional status is given at least once yearly and is not something which was mostly used in the early years of the legislation.

Figure 3.9: Overview of Exceptional Marketing Authorisations (2001-2008)

Source: DG Enterprise EC. Register of designated Orphan Medicinal Products. <<http://ec.europa.eu/enterprise/pharmaceuticals/register/orphreg.htm>>. 11/3/2009.

3.2.4 Compassionate use

Compassionate use is possible for new medicinal products to be approved through the centralised procedure of EMEA: therefore three conditions states in art. 83 of Regulation (EC) No 726/2004³⁶ must be fulfilled:

- The medicinal product is to be made available to “patients with a chronically or seriously debilitating disease, or a life threatening disease, and who cannot be treated satisfactorily by an authorised medicinal product” in the EU,
- The compassionate use programme is intended for a “group of patients”,
- The medicinal product is either “the subject of an application for a centralised Marketing Authorisation in accordance with Article 6 of Regulation (EC) No 726/2004 or is undergoing clinical trials” in the EU or elsewhere.

The aim of the compassionate use programme is to facilitate access for patients to a new medicinal product.

There are also compassionate use programmes at a national level which differ between Member States. Some of them are addressed in the next chapter.

3.3 FDA PROCESS: FROM ORPHAN DESIGNATION TO MARKETING AUTHORISATION

3.3.1 Presentation of the FDA

The Orphan Drug Act signed in 1983 was the first orphan drug legislation adopted in the world. It defines an orphan drug as a drug that is intended to treat a condition affecting fewer than 200,000 persons in the United States, or which will not be profitable within 7 years following approval by the U.S. Food & Drug Administration (FDA).³⁷

The legislation regulating the Orphan Drugs Policy in the United States can be found in the Code of Federal Regulations (CFR), Title 21, Part 316: Orphan Drugs.³⁸ The authority in charge is the Office of Orphan Products Development (OOPD) of the FDA. The OOPD’s primary objective is to promote the development of products that demonstrate promise of the diagnosis and/or treatment of rare diseases or conditions.³⁹

In order to obtain marketing approval, a drug first has to obtain Orphan Drug Designation. Up to April 2007, over 1,400 orphan products have been designated and a little more than 300 orphan products (of which 85% are drugs) have been approved since 1983.³⁷

3.3.2 Orphan Drug Designation

A sponsor can apply for the designation at the OOPD at anytime during the development process.

The product has to satisfy one of the following criteria:⁸

1. prevalence criterion: less than 200,000 persons in the US suffer from the disease; or
2. return on investment: even if there are more than 200,000 persons in the US suffer from the disease, there is no expectation that the costs of research and developing of the drug for the indication can be recovered by sales of the drug in the US.

The drug can also obtain the Orphan Designation if scientists and economists of the FDA determine that the drug will not be profitable for seven years after FDA approval, regardless of the number of patients affected.

In May 2008 there were 325 designated orphan drugs with a marketing approval of which three were approved based on the 'return on investment'-criterion.⁴⁰

The Orphan Drug Designation will not be affected by a change in prevalence of the disease.⁴¹

In order to apply for an Orphan Drug Designation, the sponsor must submit following elements to the OOPD:⁴²

- a statement requesting Orphan Drug Designation for a rare disease or condition;
- a description of the rare disease or condition, the proposed indication or indications for use of the drug, and the reasons why such therapy is needed;
- a description of the drug and a discussion of the scientific rationale for the use of the drug for the rare disease or condition;
- if an alternative already exists, an explanation why the proposed variation may be clinically superior to the first drug^m;
- if the drug is intended for a subset of persons with a particular disease or condition, a demonstration that the subset is medically plausible;
- a summary of the regulatory status and marketing history of the drug in the USA and foreign countries;
- documentation confirming one of the two abovementioned criteria;

The OOPD must formulate an answer within 60 days following the request.

The designation will give the sponsor benefits to develop a drug for a rare disease or condition. There are five incentives:

- tax credit of 50% for costs of clinical research undertaken in the USA;
- access to the OODP's clinical research grants program (even if the designation has not yet be obtained) (<http://www.fda.gov/orphan/grants/index.htm>);
- marketing exclusivity for 7 years;
- waiver of FDA user fees (always granted in the US. In the EU this in on request in EU and only for 50%);
- Development and Regulatory assistance.

^m Clinically superior is defined as having greater effectiveness or greater safety in a substantial portion of the target population or demonstration that the drug makes a major contribution to patient care (FDA's orphan drug regulations (21 C.F.R. Part 316))

Other support measures are:

- Compassionate use
- Fast track approval for a drug if (1) the condition is serious or life-threatening and (2) there is an unmet medical need for this condition. This measure does not exist as such in the EU: an expedited review or accelerated marketing approval is possible.
- Paediatric developments are exempted from user fees if they meet the criteria: paediatric patients constitute a medically plausible subset of patient population.

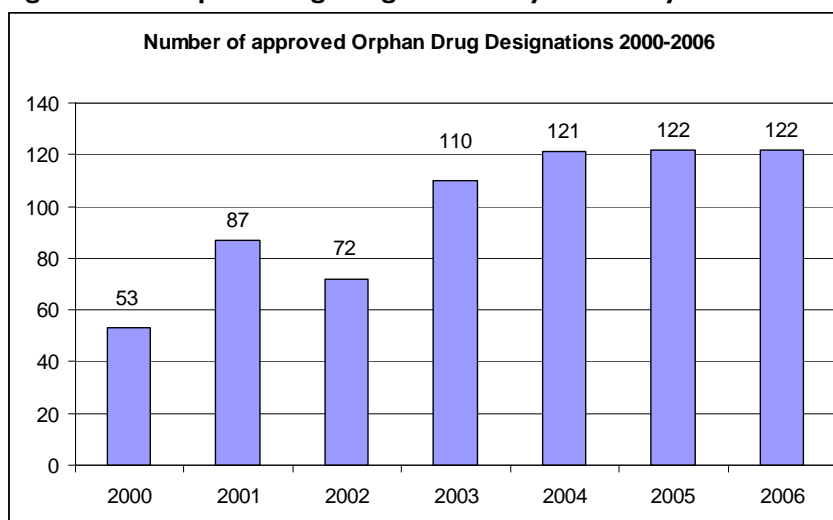
Unlike in the EU, there is no guidance for clinical trials in small populations.

A new similar drug can not obtain the same Orphan Designation unless it proves to have a clinical superiority. Clinically superior means that a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved orphan drug (that is otherwise the same drug) by showing a greater effectiveness, a greater safety or making a major contribution to patient care.³⁸

The marketing exclusivity is granted for seven years (instead of ten years in the EU), but this can be shortened if one of the following criteria applies (Section 316.31 of 21 CFR):³⁸

- the Orphan Designation is withdrawn or revoked by the FDA;
- the marketing approval is withdrawn;
- the sponsor having the exclusive approval agrees with the withdrawal;
- or the sponsor can not provide sufficient quantity of the drug.

Figure 3.10 : Orphan-drug designations – by calendar year



[Source]: Based on Lewis DY. FDA Office of Orphan Products Development - Update 2007. NORD Corporate Council Meeting 21 May 2007. Available from <http://www.rarediseases.org/info/corpcoun_powerpoint/LewisNORD52107.ppt#300,22, OOPD Moves ahead...> [Last accessed: 11/12/2008].

The sponsor will within 14 months after the designation date and annually thereafter until marketing approval submit a brief progress report to the OOPD (Section 316.30 of 21 CFR) (as in the EU).³⁸

EMA and FDA have developed a common EU/US Orphan Drug Application, but the assessments of both agencies remain different.

New is the paediatric drug development. A paediatric indication may be considered an orphan indication: the same criteria and incentives apply. But the incentives can only be used for the clinical paediatric drug development and the marketing approval can only be used for a paediatric indication.

3.3.3 Marketing approval

A marketing approval is compulsory for a drug to be distributed or transported across the United States. As this may be necessary for clinical testing of a new drug or to provide treatment with a drug showing positive results during clinical testing, the sponsor can obtain an Investigational New Drug (IND).ⁿ Once the IND is approved by the FDA, clinical trials can start.

The Marketing Approval is obtained by applying for a New Drug Application. The evaluation of the application is performed by the Centre for Drug Evaluation and Research (CDER) of the FDA and will last for ten months. Following elements are to be included in the submission file:⁴³

- non-clinical studies;
- clinical studies;
- CMC information: chemistry, manufacturing and controls;
- proposed labelling;
- additional information.

The drug will be approved if it demonstrates clinical benefit through clinical trials.

There is an accelerated approval of new drugs for serious or life-threatening diseases: these drugs provide meaningful therapeutic benefit to patients over existing treatments.⁴⁴

3.3.4 Compassionate use

Compassionate use is a method of providing experimental therapeutics prior to final marketing approval for use in humans. This procedure is used with very sick individuals who have no other treatment options. A Treatment Investigational New Drug (t-IND) can be obtained regarding some conditions:

- drug must be intended for the treatment of a serious or life-threatening disease;
- no alternative drug of treatment must be available;
- the product must be in the process of clinical trials and in an active phase of MA.

3.4 EMEA-FDA COMPARISON

The table below outlines the main differences in EMEA and FDA procedures governing Orphan Designation and Marketing Authorisation of orphan drugs.

When considering applications for Orphan Designation, EMEA focuses on the health impact of the disease, its prevalence and treatment approaches. Although FDA also examines the prevalence of the disease, this is mainly considered from the perspective of estimating the return on investment on developing a drug for the indication.

Furthermore, FDA applies a higher maximum prevalence for a disease to be designated as an orphan indication than EMEA. Unlike EMEA, the FDA does not allow reconsideration of an application for an Orphan Designation.

Market exclusivity is an incentive to entice pharmaceutical companies to develop orphan drugs as the drug would otherwise not offer a return on investment due to the low prevalence of the indication. EMEA has in place a longer period of market exclusivity than FDA. However, the European Commission can shorten this period on the request of a member state .

Both EMEA and FDA have incentives in place to apply for Orphan Drug Designation by offering the possibility to reduce or waive application fees; by offering assistance in preparing the application file; and by offering access to an accelerated review procedure.

n http://www.fda.gov/cder/regulatory/applications/ind_page_1.htm

In the USA, a tax reduction on clinical studies of orphan drugs can be granted, whereas in Europe, various financial incentives are available on a national basis.

EMA has developed specific guidance for clinical trials in small populations, which is particularly relevant to the case of rare diseases and to paediatric orphan drugs. No such guidance has been issued by the FDA.

In Europe, some countries have in place procedures governing compassionate use of orphan drugs. These procedures are outlined in the Chapter “Benchmarking of rare disease and drug markets in Europe”.

Figure 3.11: Comparison of EMA and FDA in the field of Orphan Drugs ^{45 46}

	EMA	FDA
Orphan Designation Criteria	<ul style="list-style-type: none"> - Life-threatening or chronically debilitating diseases, with prevalence < five per 10,000 population; or life-threatening, seriously debilitating or serious and chronic condition where, without incentives, there would be no justification for investing in development of treatment - No satisfactory treatment should exist or product must be of significant benefit to those with condition 	<ul style="list-style-type: none"> - Less than 200,000 persons in the USA; or there is no expectation that drug R&D costs for the indication can be recovered by sales in USA - if FDA determines that drug will not be profitable for seven years after FDA approval, regardless of number of patients affected
Reconsideration of Orphan Designation application	Yes, every 6 months	No
Prevalence	Fewer than 5 per 10,000	Fewer than 6.6 per 10,000
Institution in charge	Committee of Orphan Medicinal Products	Office of Orphan Products Development
Marketing Authorisation	<ul style="list-style-type: none"> - Application for orphan medicinal product designation - Marketing Authorisation application for orphan drug 	<ul style="list-style-type: none"> - Ask orphan drug status - OOPD - Ask Marketing Authorisation – one of the Centres of FDA
Market exclusivity	10 years (12 years for paediatric drugs)	7 years
Research funding	Money from national authorities & Community grants Private sources	Money by National Institutes of Health programmes and others Private sources
Financial incentives	Financial incentives on a national basis	Tax reduction: 50% for clinical studies
	Maximum more or less 250,000 patients affected or financially non-viable	Maximum 200,000 patients affected or financially non-viable
	Fee waiver via request: given by some Member States and by EMA for centralised applications	Always fee reduction
Assistance with	Development and Regulatory	Development and Regulatory

	EMA	FDA
application file	assistance	assistance
Accelerated marketing procedure	Possible access to accelerated review	Access to fast-track
Small populations	Guidance for clinical trials in small populations	No guidance for clinical trials in small populations
Compassionate use	<ul style="list-style-type: none"> - Procedure at EMA level for medicinal products not yet having received a Marketing Authorisation - Procedure on a national level different per member state 	A Treatment Investigational New Drug (t-IND) can be obtained

4 INTERNATIONAL COMPARISON OF RARE DISEASE AND DRUG MARKETS IN EUROPE

4.1 INTRODUCTION

The previous chapter has described the EMEA procedure from Orphan Designation to Marketing Authorisation and compared this with the FDA procedure in the United States. The present chapter describes the regulatory aspects of the rare disease and drug market in Belgium and in a number of other countries (i.e. France, Italy, the Netherlands, Sweden and the United Kingdom). A description of the regulation in each country is followed by a comparative analysis between these countries.

Key points

- **This chapter examines regulatory aspects of rare disease and drug markets in a number of countries;**
- **Regulation of the Belgian market is compared with regulation governing the Dutch, French, Italian, Swedish and British markets.**

4.2 METHODOLOGY

First, the rare disease and drug market has been described for Belgium, France, Italy, the Netherlands, Sweden, and the United Kingdom. Second, a comparative analysis was made focussing on different relevant aspects such as the institutional context, the national Marketing Authorisation procedures, pricing, reimbursement procedures, distribution channels and prescribing processes. Various elements of the institutional context were explored, including centres for rare diseases and/or orphan drugs, policy measures supporting the development of orphan drugs, and incentives for research on rare diseases and/or orphan drugs. Additionally, the analysis enquired about the criteria for compassionate use and off-label use for orphan drugs. Pricing issues related to whether a country has a system of free^o or fixed^p pricing of orphan drugs. If fixed pricing exists, the criteria for price setting were examined. The mechanism for reimbursing orphan drugs and whether orphan drugs are fully or partially reimbursed is also covered. Information was gathered about the distribution channels and site of delivery of orphan drugs. A final issue concerned the conditions for prescribing orphan drugs.

The countries were selected for their comparable living standards and their geographic proximity to Belgium. Furthermore, the chosen country panel provides insight into the variety of regulatory mechanisms that govern rare disease and drug markets. Finally, health expenditure is primarily financed by the public payer (the third-party payer or National Health Service) in each of these countries.⁴⁷

A review of the international peer-reviewed literature confirmed the absence of scientific articles on the regulation of rare disease and drug markets. Therefore, information was gained by accessing documents setting out national legislation and local publications. In addition, a qualitative questionnaire (see annex I.3) was completed by correspondents from governmental and regulatory agencies, rare disease and orphan drug national task forces, patient organisations, health insurance funds and members of the INAHTA (International Network of Agencies for Health Technology Assessment)^q. Members of the COMP at EMEA and the European Task Force on Rare Diseases also provided information.

^o In a free price system, the price is set following negotiation between the government and the sponsor.

^p In a fixed price system, the price level is fixed by the government; no deviation by the sponsor is possible.

^q http://www.inahta.org/inahta_web/index.asp

The data collection relied on a literature search, a survey based on a qualitative questionnaire and telephone interviews with national experts. Regarding Belgium, a meeting took place with Pharma.be, the representative organ of the Belgian pharmaceutical industry in order to comprehend their point of view of the Belgian situation.

Each country-specific section about the regulation governing rare diseases and drugs was validated by a national expert.

Key points

- **The benchmarking exercise focused on issues related to the institutional context, Marketing Authorisation, reimbursement, pricing, distribution and prescription of orphan drugs.**
- **Regulatory aspects of rare disease and drug markets were examined through the perusal of legal texts, the analysis of survey results, and contacts with national experts.**

4.3 BELGIUM

4.3.1 Institutional context

Belgium applies the EU definition for rare diseases. The main institutional actor in the Belgian orphan drug policy is the National Institute for Health and Disability Insurance (NIHDI). There are no official centres of reference for rare diseases, but there are several centres that are specialised in one or more rare diseases. Some of these centres are recognised by the NIHDI and work under a convention. These centres include the eight centres for human genetics⁴⁸, the seven Mucoviscidose (CF) centres, eleven centres for metabolic diseases and six for neuro-muscular diseases. The NIHDI has restricted the reimbursement of some orphan drugs to prescribers belonging to one of the recognised centres that provide treatment.

No specific programmes to fund research networks exist. There are not yet national policy measures to promote the development of orphan drugs, although there is a growing demand on the part of patients, the medical community and even politicians. Still, revenues of orphan drugs are not subject to taxation. A Pilot Group for Orphan Drugs (Stuurgroep Weesgeneesmiddelen)⁴⁹ was established in order to promote a coherent policy for orphan drugs and rare diseases. The Pilot Group comprises different thematic working groups composed of experts of different horizons. Discussed themes are survey & registries, rare diseases & costs, information & education, and reference centres. The Pilot Group has been integrated in the Fund Rare Diseases and Orphan Drugs of the King Baudouin Foundation.

4.3.2 Marketing Authorisation

Orphan drugs obtain Marketing Authorisation through the centralised procedure at EMEA since 2005 (see previous chapter). Before 2005, Marketing Authorisation through the mutual recognition procedure was till possible. In Belgium this has been the case for e.g. Duodopa.

4.3.3 Reimbursement

In order for a drug to be put on the Belgian reimbursable pharmaceutical products lists, the Marketing Authorisation Holder (MAH) has to submit a drug reimbursement request to the Drug Reimbursement Committee (DRC) of the NIHDI. Mid-February 2009, there 39 application files had been submitted of which 36 had been examined. 32 applications received a positive advice and four a negative^{r,50}. Three files were ongoing at that time. An application for reimbursement in Belgium can be submitted once the CHMP has given a positive advice,⁵¹ but companies will do this most often only after the marketing authorisation was obtained.

Figure 4.1 : Composition of the Drug Reimbursement Committee

<p>The Drug Reimbursement Committee is composed of 28 members:¹</p> <ul style="list-style-type: none"> • 22 voting members: <ul style="list-style-type: none"> ○ 7 academics ○ 8 representatives of the sickness funds ○ 4 representatives of the physicians' association ○ 3 representatives of the pharmacists association • 6 non voting members <ul style="list-style-type: none"> ○ 3 ministry representatives (Ministry of Health, of Social Affairs and of Economical Affairs) ○ 1 representative of the NIHDI ○ 2 members of Pharma.be (which is the representative organisation of the pharmaceutical industry in Belgium)

If a medicinal product is not yet on the Belgian reimbursable pharmaceutical products lists, the patient can apply for compassionate use (see point 4.3.3.2) or for reimbursement through the Special Solidarity Fund (see point 4.3.3.3).

4.3.3.1 Application procedure for reimbursement

To be added on the Belgian reimbursable pharmaceutical products lists, orphan drugs follow the same procedure as the drugs of class I and others^s (being specialties for which the company claims added therapeutic value in comparison to therapeutic alternatives) (see article 5 Royal Decree 21/12/2001)⁵², but are considered to be a specific category of drugs within class I. The procedure is the same, but the requested information is different. For example, in contrast to class I pharmaceutical products, drug reimbursement request files for orphan drugs do not have to include a cost-effectiveness analysis.

The pharmaceutical company introduces two dossiers: an application form sent to the secretariat of the DRC and a price demand to the Federal Public Service (FPS) Economy^t (see point 1.3.4 of this chapter).

^r This is the situation at that specific date and includes potentially multiple applications for a same drug (e.g. refused, then resubmitted and either approved or not).

^s There are three added value classes in Belgium. The therapeutic value of a medicinal product is decided by the DRC and expressed in an added value class.
Class 1: medicinal products of which the therapeutic added value has been proved compared to existing therapeutic alternatives;
Class 2: medicinal products with no proven therapeutic added value compared to existing therapeutic alternatives;
Class 3: other medicinal products – categorised according to legislation.

^t FPS stands for Federal Public Service known formerly as Ministry.

Once the dossier has been received by the DRC, a period of 180 days starts within which a reimbursement decision has to be taken. The dossier must contain three types of data (art. 37, RD 21/12/2001):

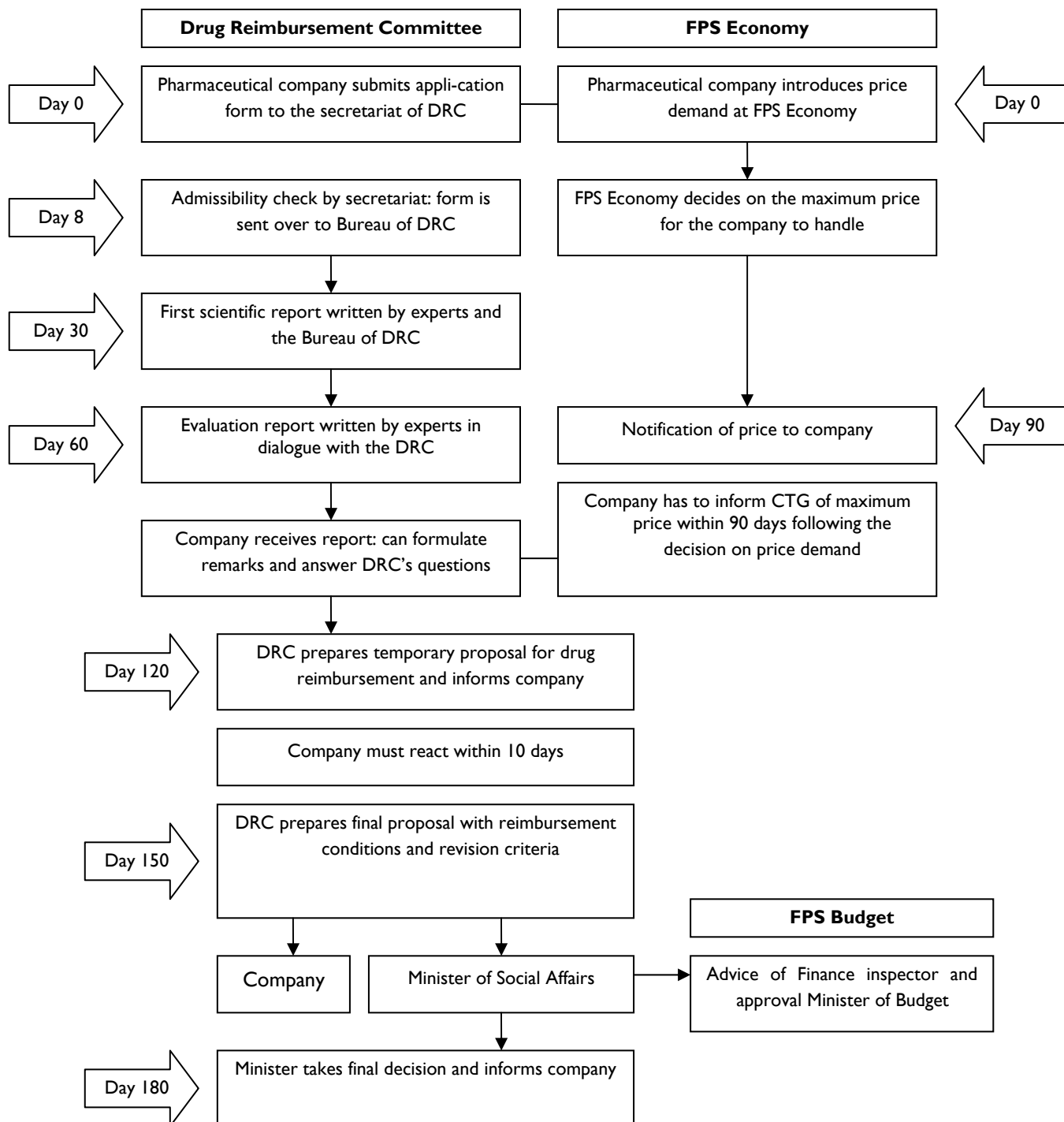
- the indication of the orphan drug as set by the Community register of orphan medicinal products and the important motivations on which the approval was based;⁵³
- a copy of the demand sent to the FPS Economy;
- a proposal regarding the reimbursement level and a justification thereof (including therapeutic value, budgetary impact and therapeutic and social needs)⁵².

The DRC may decide to compose a group of experts to evaluate the justification of the reimbursement proposal. Even if not, a first temporary evaluation report will be elaborated by the DRC (together with the experts) and sent to the company within 30 days. The final evaluation report is sent within 60 days of the dossier introduction. The company has 20 days to forward objections and remarks to the DRC, or to ask for more time to respond. (art. 15§1, RD 21/12/2001)

After having received the company's answers, the DRC prepares a temporary proposal (containing the added value class (i.e. class I), the reimbursement conditions, the reimbursement base, the reimbursement category and the revision criteria) for drug reimbursement^u if the proposal differs from the company's proposal. Otherwise the DRC will prepare a final proposal and this within a period of 150 days following reception of the application.

^u This proposal will be included in Chapter IV of the Royal Decree of 21/12/2001.

Figure 4.2 : Procedure for the inclusion of an orphan drug on the drug reimbursement list



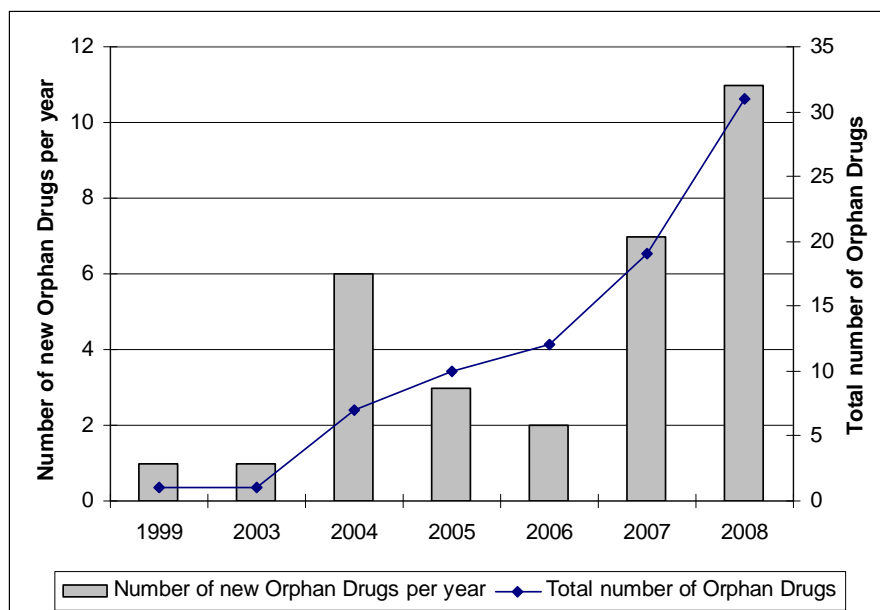
The inclusion on the reimbursement list is approved when the drug has a certain therapeutic value, being the sum of the evaluation of all the speciality's properties relevant for the treatment: this is the efficacy, the usefulness, the tolerance, the applicability and the user friendliness. Together, these elements determine the place of the speciality within the therapy compared to other available treatments. The therapeutic value is situated at the level of morbidity, mortality and quality of life. A speciality has a therapeutic *added* value if the treatment with the concerned speciality has a higher therapeutic value than the recognized standard treatment.¹⁵²

The Minister of Social Affairs will take the final decision within 180 days: he or she is not bound by the DRC's advice and can take a different decision. The Minister will ask the advice of the Inspector of Finance and receive the approval of the Minister of Budget. The Minister of Social Affairs will always follow the advice of the Minister of Budget.⁵⁰ This process is taking place during the last 30 days of the process leaving little time for negotiation. The approval of the Minister of Budget is needed because of budgetary implications giving a de facto veto right on budgetary grounds.

Current situation

On the 31st of December 2008, 31 orphan drugs were reimbursed in Belgium for a total of 35 orphan indications^v. This includes Glivec® that is approved as a Class II drug (not as a Class I as all other orphan drugs). There are several non-orphan drugs that are reimbursed for orphan indications although they do not have the Emea MA.

Figure 4.3 : Total number of reimbursed orphan drugs in Belgium 1999-2008



Source: NIHDI. Farmaceutische specialiteiten.

<http://www.NIHDI.fgov.be/inami_prd/ssp/cns2/pages/SpecialityCns.asp>. Accessed 2008-2009, 1/3/2009.

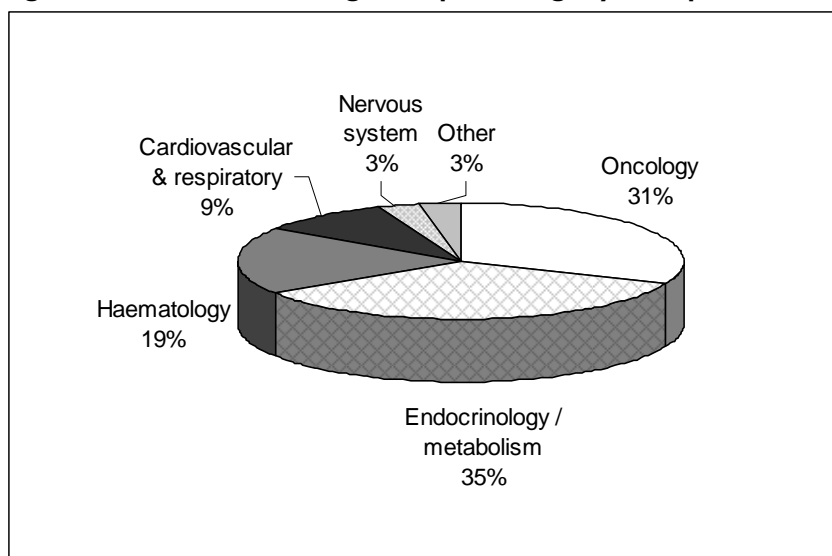
Of these 31 drugs, 30 have obtained a marketing authorisation at EU level. This means that as of 31 December 2008, there were 17 orphan drugs with a MA that were not reimbursed in Belgium. Of these 17 drugs:

- two have been approved since then (in 2009)
- two have been refused (Pedeia and Wilzin)
- one drug has probably not been submitted as there is an alternative on the Belgian market (Siklos, as Hydrea is on the market)

Of the twelve drugs left, 3 received their MA in 2008, and one can expect the manufacturers will request reimbursement in Belgium during 2009.

Orphan drugs within the therapeutic area endocrinology/metabolism account for the largest share in the total number of orphan drugs (35% of all orphan drugs are for endocrinology/metabolic conditions), followed closely by the oncology drugs (31%). Savene®, for the treatment of anthracycline extravasations, is included in the “other” category.

^v Please refer to table 9.1 in annex for the full list of orphan drugs.

Figure 4.4 : Reimbursed Belgian Orphan drugs by therapeutic area

Source: EMEA. List of orphan-designated authorised medicines 6/11/2008. Available from <<http://www.emea.europa.eu/pdfs/human/comp/56357508en.pdf>> [Last accessed: 7/5/2009].

4.3.3.2 *Compassionate use and Belgian Medical Need programme*

The Law of 1/5/2006⁵⁴ provides for compassionate use, this is the treatment with drugs which are not yet reimbursed or available in Belgium. There are two programmes:

- Programmes of compassionate use: making available, for compassionate reasons, of a medicinal product that can qualify for the centralised procedure to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must either be the subject of an application for a Marketing Authorisation in accordance with Article 6 of the European Regulation or must be undergoing clinical trials.⁵⁵
- The Medical Need Programmes: making available a medicinal product to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who can not be treated satisfactorily by an authorised medicinal product. The medicinal product concerned must have a Marketing Authorisation but
 - either the given indication has not been authorised yet, or
 - although authorised, the medicinal product is not yet available on the market in this indication.⁵⁵

The essential difference between the two programmes is that Compassionate Use concerns medicinal products which do not yet have obtained a Marketing Authorisation in Belgium, unlike the Medical Need Programme, which concerns medicinal products which have a Marketing Authorisation in Belgium for a given indication.

In order for a medicinal product to be considered for compassionate use, the MAH will have to introduce a demand that will be reviewed and approved by one of the Belgian ethics committees. The compassionate use treatment will be prescribed by a physician: the hospital can require approval for the individual patient by the local ethics committee.

4.3.3.3 *Special Solidarity Fund*

A patient can request reimbursement of an orphan drug or treatment unavailable^w in Belgium through the Special Solidarity Fund (SSF), part of the NIHDI. The objective of the SSF is the reimbursement of medical expenses for rare diseases, rare indications and innovative techniques which are not (yet) refunded by the compulsory health insurance. The legal base is the law of 27 April 2005.⁵⁶

Treatment costs for rare indications and diseases can be reimbursed if a number of criteria are fulfilled (see table below). Reimbursement will only be granted if the patient has been through all other reimbursement options, including all applicable legislation at national, European or international level. This means that reimbursement through the SSF cannot be obtained if the reimbursement of the orphan drug has been refused by the CMDOD.

Figure 4.5 : SSF's Reimbursement Criteria

Type of reimbursement	Reimbursement criteria
Reimbursement of treatment costs for rare indications (art. 25 bis)	<p>The treatment is expensive.</p> <p>Medical treatment is prescribed by a medical doctor specialised in the treatment of the related disorder and authorised to practice medicine in Belgium.</p> <p>Medical treatment has a scientific value and effectiveness which is largely recognized by the medical profession. The medical treatment has to have outgrown the experimental phase.</p> <p>The compulsory health insurance system cannot provide an alternative.</p> <p>Medical treatment is used for an indication threatening vital functions of the patient.</p>
Reimbursement of treatments costs for rare diseases (art. 25 ter § 1)	<p>The medical treatment is considered as being expensive.</p> <p>The compulsory health insurance system does not provide a therapeutic alternative treatment.</p> <p>Medical treatment is used for a rare disease that threatens the vital functions of the patient.</p> <p>The medical treatment is prescribed by a medical doctor specialized in the treatment of the specific disease and authorised to practice medicine in Belgium.</p> <p>The medical profession recognizes the treatment as the specific approach for the rare disease.</p>
Reimbursement of cost for rare diseases requiring a continuous and complex treatment (art. 25 ter § 2)	<p>Treatment as a whole is expensive.</p> <p>Treatment is related to a threat of the vital functions of a patient.</p> <p>The threat of the vital functions is directly and specifically a consequence of the rare disease.</p> <p>The compulsory health insurance system does not provide therapeutic alternative.</p> <p>The complex treatment is prescribed by a medical doctor, specialized in the treatment of the specific disease and authorised to practice medicine in Belgium.</p>

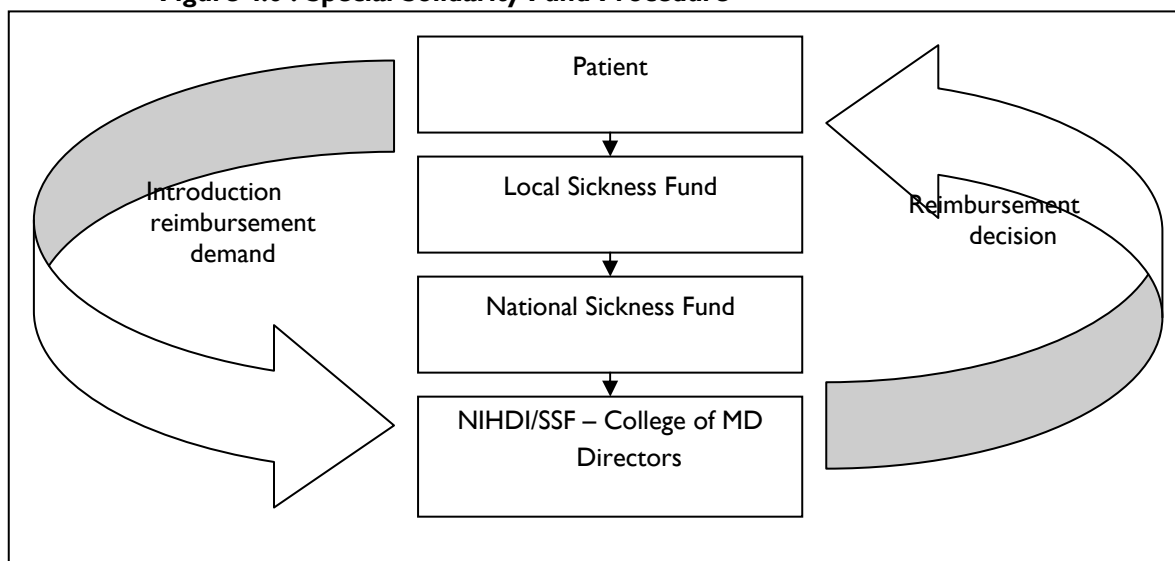
Source: NIHDI. Het Bijzonder Solidariteitsfonds. Wat is de functie ervan? Wanneer en hoe kunt u er een beroep op doen? 2006. Available from <<http://www.inami.fgov.be/care/nl/infos/solidarity/pdf/fss20060424.pdf>> [Last accessed: 14/4/2008].

^w Whether or not this orphan drug has a MA or is reimbursed abroad.

The NIHDI body responsible for managing the SSF and taking decisions about reimbursements is the College of Medical Doctors Directors composed of Medical Doctor Directors of each national sickness fund and of NIHDI MDs.

The patient's Medical Doctor (MD) (a specialist) will fill out a form and hand it over to the health insurance institute through the local and national sickness fund. Within one month, the College of MD directors will examine the application and take a decision. The decision is transmitted to the patient and to the local sickness fund. In case of a positive advice, this latter will proceed to the reimbursement within fifteen days. The request for reimbursement must be done within three years following the end of the treatment.

Figure 4.6 : Special Solidarity Fund Procedure



NIHDI = National Institute for Health and Disability Insurance; SSF = Special Solidarity Fund

The SSF has in 2007 reimbursed five drugs with Orphan Designation (not yet reimbursed as orphan drugs) for 141 patients for a total amount of € 4 084 225 (€ 28 966 per patient). This accounts for 35% of the SSF's budget. The table below gives an overview of these five drugs. From the five products, five have been approved for reimbursement as orphan drugs since.

Figure 4.7 : SSF reimbursement for Orphan Drugs with MA in 2007

Orphan drug	Total NIHDI Expenditures	Number of patients	NIHDI expenditures per patient
Myozyme®	€ 3 540 723	7	€ 505 818
Revatio®	€ 299 358	67	€ 4 468
Revlimid®	€ 141 050	57	€ 2 475
Ventavis/Iloprost®	€ 100 927	9	€ 11 214
Tracleer®	€ 2 167	1	€ 2 167

Source: NIHDI. Jaarverslag 2007 betreffende het Bijzonder Solidariteitsfonds, 2008

4.3.4 Pricing

The pharmaceutical company introduces a price demand at the Federal Public Service (FPS) Economy^x at the same time a reimbursement demand is introduced. This application consists of¹

- name and address of the MAH;
- name, pharmaceutical form, accurate indication and (if applicable) therapeutic added value of the drug;
- a statement of registration proof, the scientific instruction leaflet and the public instruction leaflet;
- a justification for the proposed price in terms of cost drivers;
- the annual accounts of the applicant for the last three years;
- the market and competition conditions and a price comparison with other EU Member States.

The information to be provided for orphan drugs is the same as for non orphan drugs. Still, the evaluation might differ according to the actual information provided as there are no standard reporting requirements for costs imposed.

The FPS Economy compares the given information with available data (such as other drug dossiers, other countries and other similar therapeutic drugs).⁵⁰

Within a period of 90 days the FPS Economy will decide on a price and inform the company. The company must notify the price to the Drug Reimbursement Committee. The Committee takes that into account when making a reimbursement decision.

No exchange of information takes place between the FPS Economy and NIHDI during this period. Following the decision, the FPS Economy will play no other role but to collect the manufacturers' turnover figures.

4.3.5 Distribution

Most orphan drugs, except for two (Glivec and Thalidomide) are distributed through the hospital pharmacies.

4.3.6 Prescribing

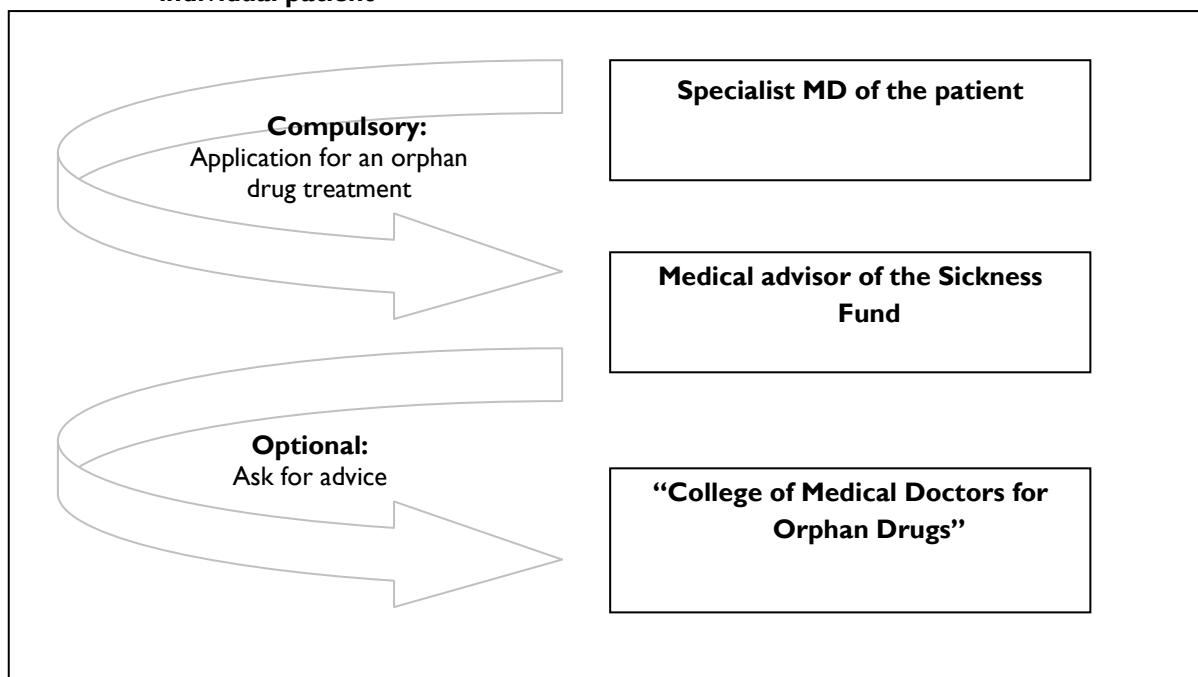
The prescription of orphan drugs is subject to conditions to be found in the reimbursement form. Orphan drugs are part of the reimbursement category A^y: these are drugs for severe conditions or diseases and are reimbursed at 100%. The conditions for reimbursement are described in the applications forms for reimbursement to be found in Chapter IV of the Royal Decree of 21/12/2001.⁵² This chapter contains all drugs that receive special reimbursement conditions due to medical and/or budgetary reasons.

A physician wishing to prescribe an orphan drug to a patient has to follow the procedure set out in Figure 4.8 in order to obtain reimbursement for this patient. The physician must receive the approval of a Medical Advisor of the sickness fund. This procedure also applies to a number of non-orphan drugs and is hence not specific for orphan drugs. However, in case of orphan drugs the medical advisor has the additional possibility to ask advice from the "College of Medical Doctors for Orphan Drugs" (CMDOD) if one exists for the drug. The Medical Advisor of the sickness fund can, but is not obliged to, request the advice of the CMDOD.

x FPS stands for Federal Public Service known formerly as Ministry.

y This categories define the reimbursement level and are different to the Classes mentioned above, which are based on the therapeutic value. Orphan drugs are automatically classified into the highest reimbursement category (100%) and in Class I.

Figure 4.8: Procedure to request reimbursement of orphan drug for an individual patient



Source: FOD Sociale Zekerheid. Koninklijk besluit van 8 juli 2004 betreffende de vergoeding van weesgeneesmiddelen. Belgisch Staatsblad, 20/07/2004.

Individual reimbursement advice is formulated on a case by case basis by the CMDOD if their involvement is required by the reimbursement modalities of the orphan drug. It is the DRC that decides whether or not a College is established. At the end of April 2009, there were eighteen colleges for 31 orphan drugs.

A College is composed of a president, four specialist MDs in the indication/disease and four MDs member of the DRC and mandated by a sickness fund.²⁰

It is the specialist MD of the patient who completes an application form for the orphan drug to be found in Chapter VI of the Royal Decree of 21/12/2001⁵², and who submits the application to the sickness fund. It is imperative that the MD is affiliated to a recognised centre or a hospital for a certain disease, e.g.:

- for metabolic diseases : a Revalidation Centre for monogenetic hereditary metabolic diseases;^z
- for haematology: a Centre for Haematology linked to a hospital;
- for cardiology-pulmonology: a hospital.

The Medical Advisor of the sickness fund will examine the demand and can decide to request the advice of the CMDOD. Even if the Medical advisor is is not obliged to request the advice of the CMDOD of the concerned orphan drug, in practice he or she for each decision^{aa} always asks for advice.⁵⁷ The CMDOD formulates its advice based on the reimbursement criteria defined in Chapter VI of the Royal Decree of 21/12/2001.

The demand for individual reimbursement has to be introduced every year as reimbursement approval is only valid for a period of twelve months.

^z <http://www.NIHDI.fgov.be/care/all/revalidatie/general-information/contacts/pdf/7890.pdf>

^{aa} The pharmaceutical industry claims that not all reimbursement demands are submitted to the CMDOD. There is no evidence to confirm this statement.

Key points

- In Belgium, there are no specific centres of reference, policy measures, research incentives on rare diseases/orphan drugs.
- Orphan drugs are registered through the EMEA centralised procedure only. Specific legislation governs compassionate use of orphan drugs and there exists a programme for medical needs.
- Orphan drug maximum prices are fixed by the Federal Public Service Economy as is the case for all drugs, independently of the reimbursement decision.
- The reimbursement procedure considers budget impact, but not cost-effectiveness. Pharmaceutical companies do not have to submit a formal cost-effectiveness analysis as part of a drug reimbursement request file for an orphan drug. Orphan drugs are fully reimbursed by the NIHDI.
- Orphan drugs are distributed through hospital pharmacies only.
- The prescription of orphan drugs by specialist physicians is subject to approval of a Medical Advisor of the sickness fund and in practice based on the advice of a College of Medical Doctors for Orphan Drugs.

4.4 FRANCE^{bb}

4.4.1 Institutional context

Three institutions play a role with regard to orphan drugs on the French market: the French Agency for the Sanitary Security of Health Products (Afssaps - Agence Française de Sécurité Sanitaire des Produits de Santé), the High Health Authority (HAS – Haute Autorité de Santé), and the Ministry of Health. The HAS is a public independent authority having as objectives to improve the quality and security of the health services, to maintain a high-performance health system and to inform patients on their diseases and treatment.

The institution in charge of research on rare diseases is the GIS^{cc} – Institut des Maladies rares whose objectives are to define and establish a national policy for research on rare diseases; to mobilise the competences and to enhance multidisciplinary approaches; and to coordinate the research and to associate existing means.⁵⁸

Measures taken to promote the orphan drug policy of the EU:

- 2001: The pharmaceutical companies promoting orphan drugs are exonerated from the taxes and contributions pharmaceutical companies owe to the Sickness Insurance and the Afssaps.⁵⁹
- 2002: A special funding for commercialised orphan drugs is integrated in the hospitals' budget for innovative drugs.⁵⁹
- 2006: Recognition of the “Fédération des Maladies Orphelines”^{dd} as the only publicly recognised representative^{ee}.

Measures taken to increase the knowledge about rare diseases:

- 2000-2005: the network ‘Genhomme’ was established to provide an answer to the scientific and economical challenges of the human genomics.
- 2001: establishment of the “Plateforme Maladies Rares” grouping all actors devoted to patients with rare diseases.
- 2001: establishment of the “Comité de Génétique Clinique” to support research and care treatment in the field of genetics.

^{bb} This chapter has partly been reviewed by Ms Annie Lorence of the Afssaps.

^{cc} Groupe d'intérêt scientifique

^{dd} <http://www.maladies-orphelines.fr/>

^{ee} In French: “reconnue d'utilité publique”

A French National Plan for Rare Diseases with ten strategic priorities was published in 2004. The aim is to assure equal access to diagnostic, treatment and care taking of persons suffering of a rare disease through implementation of ten strategic priorities. A new draft is being prepared at the moment.

One of the strategic priorities is to enhance care management through the establishment of centres of reference.⁶⁰ Mid-February there were 131 centres of reference who were awarded the label by the Health Minister for five years. The centres have a double role: they are an expert centre for 1 or more diseases and they are a resource centre for patients coming from outside the region. A second type of centres are the qualified centres whose aim is to assume responsibility for treatment and follow-up of the patient close to their home, and to participate in the entirety of the centres of references' tasks. These qualified centres take in charge patients that can not be treated in a reference centre.⁶¹

There are several incentives to stimulate orphan drug development:⁶²

- Research support through national funding programmes: GIS-Rare diseases, Hospital Programme of Clinical Research (*Programme Hospitalier de Recherche Clinique*);
- During development: Free scientific advice of Afssaps;
- Budgetary incentives: tax exemption of the Sickness Insurance and the Afssaps.

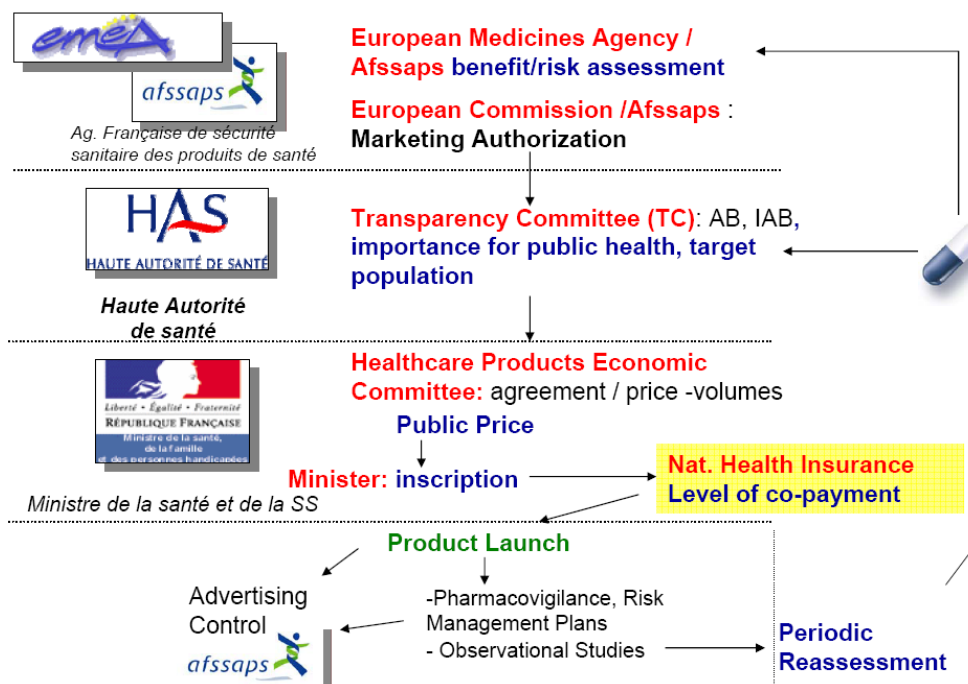
4.4.2 Marketing Authorisation

Orphan drugs obtain Marketing Authorisation through the centralised procedure at EMEA (see previous chapter).

4.4.3 Reimbursement

After having obtained a Marketing Authorisation of EMEA, the MAH will introduce a demand for reimbursement at the HAS.

Figure 4.9 : Introduction process of orphan drug in France: 2 steps



Source: Meyer F. Orphan Drugs: How Are They Assessed / Appraised in France? In: HAS (ed). 25 February 2008, p.4.

The demand for inclusion on the reimbursement list is examined by the Transparency Committee of the HAS. The Transparency Committee renders an advice on the clinical added value (SMR: Service Médical Rendu) and the improvement in the clinical added value (ASMR: Amélioration du Service Médical Rendu) as compared with existing therapies. The Committee then proposes a positive or negative advice to the Health and Social Security Ministers relating to the reimbursement of the drug.

There are two criteria for inclusion in the reimbursement list:⁶³

1. Clinical added value: takes into account the indication (disease characteristics and severity) and the drug characteristics (clinical effectiveness and impact on public health). If the added value is insufficient, no reimbursement takes place.
2. The improvement of clinical added value: this is the clinical improvement compared to existing therapies. There are five levels
 - ASMR Level I, II and III: innovative drugs (recognized added value) are eligible for faster access at a better price;
 - ASMR Level IV: minor improvement – product eligible for a higher price than comparators;
 - ASMR Level V: no improvement – reimbursement possible if costs are inferior to comparators.

The Ministry of Health decides on the reimbursement of the drug.

In figure 4.10, the first table provides an overview is given of the SMR since 2002 and of the ASMR for 2007. Since 2002, 35 orphan drugs have received a favourable clinical added value. The second table shows that orphan drugs score better on the ASRM level than non-orphan drugs.

Figure 4.10 : Overview of the assessment of orphan drugs in France

SMR (since 2002)	
Year	N
2002	1
2003	6
2004	5
2005	3
2006	6
2007	12
Total	35

Level ASMR 2007 for orphan and non-orphan drugs		N	% OD	% all drugs
ASMR I	Major	3	10%	1%
ASMR II	Important	13	43%	4%
ASMR III	Moderate	8	27%	6%
ASMR IV	Minor	4	13%	5%
ASMR V	No improvement	2	7%	84%
		30		

Source: Meyer F. Orphan Drugs: How Are They Assessed / Appraised in France? In: HAS (ed). 25 February 2008, p.12.

The Transparency Committee also:⁶⁴

- Makes an estimate of the target population;
- Gives advice to the prescribers on the drug's place within therapy;
- Determines the limits of the currently available data and request additional data.

Another actor intervening in the reimbursement decision is the National Health Insurance Fund. It

- fixes reimbursement rates for drugs within the conditions and limits fixed by the State;
- classifies drugs into categories on the basis of the National Health Authority assessment of the clinical added value;
- decides which acts and performances will be reimbursed.⁶⁵

4.4.3.1 *Compassionate use*

Orphan drugs can be delivered to patients without having first received a Marketing Authorisation, through clinical trials, authorisation for temporary usage (ATU) and hospital preparations. Experimental drugs can be administered in clinical trials and to hospital preparations for which there is no pharmaceutical speciality available or adapted. Furthermore, innovative drugs may receive an ATU of the Afssaps if there is a public health need. The drug must fulfil several criteria: it is a treatment for a serious or rare disease; no therapeutic alternative is available; it has a positive risk/benefit and it is for temporary use. The evaluation will take into account aspect of the drug (quality, security and efficacy) and the medical environment (disease and alternatives). Examples or medicinal products that use the ATU are: Thalidomide®, Aldurazyme®, Cerezyme®, Fabrazyme® and Carbaglu®.⁶⁶

4.4.3.2 *Off-label use*

Off-label use of an orphan or non-orphan drug is possible for a rare disease (as defined by the European Regulation 141/2000⁵) if the medicinal product is listed in an advice or recommendation relating to a category of sick persons of the HAS (Article L162-17-2-1 of the Social Security Legal Code).

The treatment and reimbursement are decided by decree of the Ministers of Health and Social Security and following advice of the National Union of the Sickness Funds. The specialities, products or services being the subject of the decree can be dealt with only if their use is essential to the improvement of the health of the patient or to avoid its deterioration. They must moreover be registered explicitly in the protocol of care.

4.4.4 Pricing

The Economic Committee for Health Products of the Ministry of Health negotiates the price of an orphan drug with the pharmaceutical company in order to reach an agreement on the price-volume.⁶⁷

Price setting for an orphan drug takes into account:⁶³

- the improvement in clinical added value of the medicine;
- the prices of medicines serving the same therapeutic purpose;
- forecasted or recorded sales volumes;
- foreseeable and actual conditions of use of medicine;
- the National Health Authority assessment;
- reference prices in Ireland, Italy, Portugal, Spain and the EU.⁶⁸

4.4.5 Distribution

Orphan drugs are distributed through the community pharmacies or the hospital pharmacies. For one third of the orphan drugs prescription by and delivery through the hospital pharmacy for hospitalised patients is obligatory.

4.4.6 Prescribing

The orphan drug will be reimbursed if the rare disease is one of the indications. Otherwise, the drug can still be prescribed, but it is not reimbursable.⁵⁹

The prescription must be delivered by a MD specialist either working on its own (minority of orphan drugs) or within a hospital (majority of orphan drugs). But the first prescription has to be delivered by a centre of reference (if such centre exists for the disease at issue).

It is the Social Security that is in charge of reimbursement.

Key points

- **France has in place specific centres of reference, policy measures, and research incentives on rare diseases/orphan drugs.**
- **Orphan drugs are registered through the EMEA centralised procedure. Specific legislation governs compassionate use of orphan drugs.**
- **Orphan drug prices are fixed by the Economic Committee for Health Products of the Ministry of Health.**
- **The reimbursement procedure considers the clinical added value. Orphan drugs are fully or partially reimbursed by social insurance.**
- **For some orphan drugs, prescription and delivery through hospital pharmacies is compulsory.**

4.5 ITALY^{ff}

4.5.1 Institutional context

The Italian Medicines Agency (AIFA - Agenzia Italiana del Farmaco) is in charge of the introduction of orphan drugs on the Italian medicine market. The AIFA has also set up a fund of around 45 millions Euro a year, of which half is used to the reimbursement of orphan and 'life saving' drugs and the other half is aimed at supporting independent research, drug information programs and pharmacovigilance.⁶⁹ This funding program for independent clinical research on drugs is open to researchers working in public and non profit institutions. One of the research areas of the program is dedicated to orphan drugs for rare diseases. At the start of 2009, three calls for proposals (2005-2007) have been concluded and 69 studies have received funding in the area of rare diseases.

Several incentives for promoting non-profit research were issued in an ad hoc regulation of 2004:

- the fees of the ethics committee are waived;
- the National Health Service (NHS) can reimburse the study drugs;
- and patients' insurance costs are financed by the study institution.⁶⁹

In every Italian region there are one or more Regional Centres, which act as reference centres in the region and are authorised to diagnose rare diseases and to prescribe orphan medicines. There is also a National Centre for Rare Diseases at the National Institute of Health, which coordinates the activity of the regional centres, carries out scientific research and public health activities, including cooperation with patient associations.⁷⁰

Three National Healthcare Plans (1998-2000; 2003-2005; 2006-2008) and Regional Health Plans were formulated where rare diseases were addressed. The first National Plan has defined rare diseases as a priority for public health.

^{ff} This chapter has been reviewed by Dr. Pietro Folino Gallo of the Italian Medicines Agency.

A National Network for Rare Diseases and a National Registry of Rare Diseases were established in 2001.⁶⁰ The National Network is composed of a network of hospitals and referral centres organised by region where patients can be diagnosed and treated for free for about 500 rare diseases. The aims⁷¹ of the Network are:

- Prevention: implementation of prevention activities,
- Surveillance: develop epidemiological surveillance,
- Diagnosis: implement both diagnosis and care intervention,
- Treatment: improve health operators' training,
- Promote citizens information.

The National Registry of Rare Diseases is to be completed by regional centres. The registry's general objectives are national and regional health planning and surveillance of rare diseases. The specific objectives are the estimation of incidence and/or prevalence, the definition of standardized diagnostic and therapeutic protocols, and the improvement of the collaboration among health care operators.

4.5.2 Marketing Authorisation

Orphan drugs obtain Marketing Authorisation through the centralised procedure at EMEA (see previous chapter).

4.5.2.1 *Compassionate use*

Compassionate use of orphan drugs waiting for approval is possible and financed through a special fund called "Fondo AIFA 5%". The aim of this fund is threefold: to improve knowledge on efficacy and safety of orphan drugs; to improve knowledge on efficacy and safety of non-licensed / non-marketed orphan drugs and to promote access to orphan drugs waiting for a Marketing Authorisation.⁷²

This not only applies to orphan drugs, but also to trials on rare diseases.

In 2008, four orphan molecules were reimbursed by the NHS through the Fondo AIFA 5%.

4.5.2.2 *Off-label procedure*

Italy also knows an off-label procedure regulated by Law 648/96. The Technical Committee of the AIFA can include a given medication into a special list allowing it to be prescribed at NHS (National Health Service) charge, if for a specific disease there is no therapeutic alternative. There are three types of medical products that can be included:

- innovative drugs whose sale is authorised abroad, but not in Italy;
- drugs not yet authorised but which underwent clinical trials;
- and drugs to be used for a therapeutic indication other than the one which has been authorised.

At present fourteen orphan molecules are reimbursed for rare diseases in off-label use by the NHS.⁷³

4.5.3 Reimbursement

Orphan drugs that have obtained an EMEA Marketing Authorisation can apply for reimbursement in Italy.

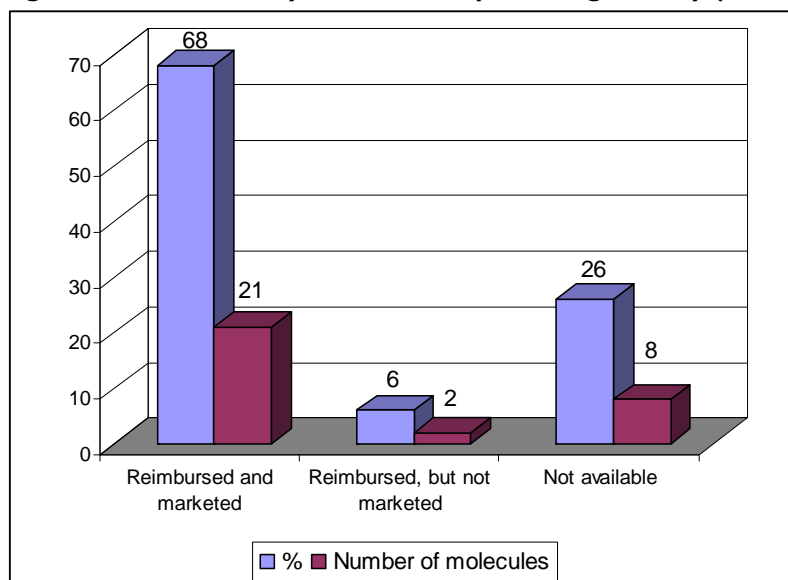
In order to be reimbursed, any medical products, including orphan drugs, has to meet a number of criteria:

- it covers an unmet need being a relevant disease without any efficient therapy;
- existing therapies for a relevant disease are not satisfactory;
- the product has a better benefit-risk ratio than existing therapies;
- it has a socio-economic benefit.⁷²

These criteria are evaluated at the Scientific-Technical Committee (Commissione Tecnico-Scientifica) and at the Pricing and Reimbursement Committee. Both these Committees are consultative bodies within the Italian Medicines Agency.

Because, by definition, an orphan drug covers an unmet need, most of the orphan drugs are at the charge of the Italian NHS.

Figure 4.11 : Availability of licensed orphan drugs in Italy (October 2007)



Source: Folino Gallo P. Orphan Drugs in Italy. Accommodating orphan drugs: balancing innovation and financial stability. Accommodating orphan drugs: balancing innovation and financial stability; 25 February 2008; London.

4.5.4 Pricing

Two committees of the Italian Medicines Agency are involved in the pricing and reimbursement procedure of medical products. The Scientific-Technical Committee takes decisions if a medical product can be reimbursed and positive list revisions, while the Pricing and Reimbursement Committee assesses the applications and negotiates with the MAHs according to the mandate received by the Scientific-Technical Committee.

The procedure for pricing pharmaceutical products reimbursed by the NHS is fixed by law. First, the Scientific-Technical Committee decides whether or not a product can be reimbursed. If yes, a price negotiation takes place between the Pricing and Reimbursement Committee and the MAH. If the negotiation turns out positively, the product will be reimbursed.

The product will then be listed in one of three drug classes: class A includes essential products and products for chronic diseases that are 100% reimbursed by the NHS; class H includes products that are 100% reimbursed through the hospital; and class C includes all other products which are not reimbursed because the health authorities intend to discourage their use (these products have a low evidence level and/or a low benefit / risk ratio).

Medicines included in class C are for example antiobesity agents and benzodiazepines. Products for minor ailments are not reimbursed.

Products of class C can still be used for free at a hospital level.

Price determination criteria are:⁶⁸

- the efficacy of the product in relation to existing therapies, taking into account its degree of innovation, the clinical relevance, incidence and prevalence of the disease it intends to treat, possible reductions in hospitalisation, and quality of life improvements;
- price comparisons with other countries (but a formal external price reference system was withdrawn in 2004);
- forecasts of sales, including revenues derived from licensing agreements;
- financial factors, related investment, spill over effects on employment, and exports.

Prices are generally revised after two years, but both AIFA and company can at any moment request a revision of the contract. The company can even lower the price without permission, for instance after patent expiration and the introduction of a generic competitor, but a notification of the new price is needed.

4.5.5 Distribution

Orphan drugs are distributed through hospital and community pharmacies, and by health authorities.

4.5.6 Prescribing

The orphan drug is prescribed by a specialist MD member of a centre of reference.

A control mechanism exists for some rare diseases under the form of national registers (which are not much populated). AIFA also has a tracking system (traceability) for monitoring the movement of every pack (including orphan drugs) from the manufacturer via the wholesale to the hospitals and pharmacies. Some regions have local systems to match the prescriber/dispenser and the patient.

Figure 4.12 : Orphan Drugs subjected to registration

Aldurazyme®	Orphan Drug Register
Cabarglu®	Orphan Drug Register
Myozyme®	Orphan Drug Register
Somavert®	Orphan Drug Register
Ventavis®	Orphan Drug Register
Zavesca®	Orphan Drug Register
Nexavar®	Oncologic Register
Xagrid®	Oncologic Register
Sutent®	Oncologic Register

Source: Folino Gallo P. Orphan Drugs in Italy. Accommodating orphan drugs: balancing innovation and financial stability. Accommodating orphan drugs: balancing innovation and financial stability; 25 February 2008; London.

Conditions may be applied to the prescription of orphan drugs. One of these conditions is the registration of the treatment into a national register (especially for cancers). This means that the hospital doctor must list the patient into the register and complete the appropriate form (registration, treatment start, follow-up, ...). Hospital pharmacists can dispense the orphan drugs only upon a written request with attached the register sheet.⁶⁹

In some regions a dispensation fee of around 2 Euro is imposed, but patients with a rare disease are generally exempted from this fee.

Key points

- Italy has in place specific centres of reference, policy measures, and research incentives on rare diseases/orphan drugs.
- Orphan drugs are registered through the EMEA centralised procedure only. Specific legislation governs compassionate use and off-label use of orphan drugs.
- Orphan drug prices are fixed by the Pricing and Reimbursement Committee.
- The reimbursement procedure considers budget impact and cost-effectiveness. Orphan drugs are fully reimbursed by the National Health Service.
- Orphan drugs are distributed through hospital and community pharmacies, and by health authorities.
- The orphan drug is prescribed by a specialist MD member of a centre of reference. Conditions, such as registration of the treatment in a national register, are applied to the prescription of orphan drugs.

4.6 THE NETHERLANDS^{gg}

4.6.1 Institutional context

The applicable rare diseases definition in the Netherlands is the EU definition.

The institution in charge of rare diseases is the Ministry of Health.

There are no official centres of rare diseases, but the eight university medical centres fulfil the role of main clinical expertise centres for specific rare diseases and can function as centres of specific rare diseases. For some rare diseases also other (top clinical) hospitals may function as centres for rare diseases.

Several policy measures were taken in order to promote the development of orphan drugs:⁷⁴

- A Steering Committee Orphan Drugs was established in 2001 in order “to encourage the development of orphan drugs and to improve the situation of patients with a rare disease, especially to strengthen the transfer of information on rare diseases”.^{hh} The Committee is also a member and work package leader of the European project European (European Project for Rare Diseases National Plans Development, 2008-2011) that is preparing recommendations for the Member States on how to write a national plan on rare diseases and orphan drugs.
- An orphan product developer was appointed in 2006 within the Dutch Organisation for Health Research and Development (ZonMw)ⁱⁱ to inform academia and enterprises (especially SME’s) about the European Regulation on Orphan Medicinal Products in an active way (by means of visits, seminars, articles, etc.). This person (R. de Rue) has been appointed for four years. After that it will be examined if the function can be handed on to the Medicines Evaluation Board or to an industry platform.

gg This chapter has been reviewed by Dr. Sonja van Weely of the Dutch Steering Committee Orphan Drugs and Dr Gepke Delwel of the Health Care Insurance Board

hh www.weesgeneesmiddelen.nl

ii www.zonmw.nl

- A PhD student (H. Hoekstra) was appointed in 2005 in order to study the factors of success and failure in orphan drug development and this in close collaboration with the Steering Committee and the orphan drug developer.⁷⁵
- The Dutch registration fee for a medicinal product can be waived if the medicinal product is already registered in one or several other EU Member States and the prevalence of the indicated disease is less than 1 in 200,000 inhabitants in the Netherlands.
- In 2007 a new research programme for rare diseases and orphan drugs was developed in order to develop therapies for rare diseases, but no formal decision of the Ministry of Health on the funding of this programme has been taken until now.
- An Orphan Drug Designation Support Programme was launched in January 2009: Dutch enterprises can apply for a grant to compensate the application costs for the EMEA Orphan Drug Designation.^{jj}
- In April 2009 the Dutch Orphan Registry Consortium was launched, a multidisciplinary group that will use best practices to build a registry frame work for inborn errors of metabolism.

The Netherlands (represented by Zoom and the Steering Committee) are partner in E-Rare (ERA-Net for research programmes on rare diseases)⁶⁹, a research network funded by the European Commission, providing a setting to bring together clinicians and scientists and gather research infrastructure, patient cohorts and related biological material on a European scale. Zoom is the leader of work package 5 that focuses on the opening of programmes to encourage a multidisciplinary approach.

Zoom provides funding through several research programmes for research on rare diseases, e.g.

- The Innovative Research Incentives Scheme;
- The Gene Therapy subsidy scheme.

Information on rare diseases and orphan drugs is disseminated by different actors:

- Royal Dutch Society for Pharmacists (KNMP) created the website www.farmanco.knmp.nl where information on European registered orphan drugs can be found with information on their reimbursement in the Netherlands;
- Patient organisations for (a group of) rare diseases (they can obtain funding indirectly from the Ministry of Health).

4.6.2 Marketing Authorisation

There is no national procedure of Marketing Authorisation for orphan drugs. All orphan drugs have to be registered at the EMEA, but the Medicines Evaluation Board (MEB) is involved in evaluating orphan drugs for the EMEA. As an independent medicinal products knowledge centre, the MEB evaluates the balance efficiency-safety (this is efficiency, risks, quality) of drugs for humans and animals, thus the advantages versus disadvantages.⁷⁶ The MEB's report contains product information for MD and pharmacist and an instruction leaflet for the patient. The MEB will continue to follow-up information on the drug even after it entered the market.

jj <http://www.zonmw.nl/nl/subsidie/subsidiekalender/subsidieronde/item/subsidieregeling-orphan-designation-dossier-odd-support/>

Compassionate use

There is no specific policy for orphan drugs, but there is a general policy for compassionate use. In exceptional cases, compassionate use is possible if:⁷⁷

- There is a MD declaration (named patient);
- It concerns a serious condition for which no alternative drug is on the market and of which the drug is awaiting a Marketing Authorisation. In that case, the MAH can apply for 'the compassionate use programme'.

Off-label use

The off-label procedure is the same for orphan drugs and non-orphan drugs. Off-label use is accepted if scientific evidence attests of an added value of the treatment with the drug, the drug is rational and justified, but which has not (yet) been evaluated by the MEB.⁷⁸ The patient must be informed of the off-label treatment.⁷⁸

4.6.3 Reimbursement

Extramural drugs, i.e. drugs that are prescribed by General Practitioners and are used in the out-patient setting, can apply for reimbursement after the registration. All manufacturers do apply for reimbursement at the Ministry of Health. Consequently, the Health Care Insurance Board (HCIB) will perform the assessment and appraisal procedure for the drug based on the submitted dossier by the manufacturer. Most drugs are reimbursed; co-payments are possible but are rare in the Netherlands.

Intramural drugs or hospital-based drugs i.e. drugs that are prescribed by medical specialists within hospitals are paid by the hospital budget. All medical products that are included in the official treatment guidelines of the physicians are available to patients and have to be paid for by the hospitals. Since hospital budgets are limited, it is difficult to ensure equal access of expensive drugs to all patients. To overcome this 'postcode prescription' by hospitals, policy measures have been issued. Through these policy measures expensive hospital-based (orphan) drugs can apply for additional funding. Orphan drugs that are listed on the policy measure will get a full funding, so the costs for these drugs are fully covered by means of those additional budgets. In case of expensive hospital based drugs a 80% funding is provided to the hospitals. Hospitals can apply for additional funding at the Dutch Care Authority (NZa). The HCIB will subsequently assess and appraise the request based on the submitted dossier by the applicant (hospitals, physicians and manufacturer are involved). The additional funding is always conditional, i.e. temporally, additional information needs to be collected through outcomes research. After three years a reassessment takes place in order to assess whether listing / funding will continue.

The assessment and appraisal procedures for extramural and intramural drugs are different: reimbursement versus additional funding and assessment versus a two tiered process based on coverage with evidence. The assessment criteria are not very different. For extramural drugs the HCIB assess the therapeutic value of the drug in comparison with the existing standard treatment - assessment of the place of the new drug in the therapy; the cost-effectiveness of the drug and the budget impact of the drug for the pharmacy budget. For intramural drugs, the assessment criteria for temporally listing are the therapeutic value, the cost prognosis, the cost-effectiveness indication and the proposal for outcomes research. After three years the reassessment criteria are: the therapeutic value; the actual costs of the medical product; the cost-effectiveness and the efficient prescription. The efficient prescription of the drug in Dutch hospitals is based on data collected through outcomes research in the Dutch clinical practice. Also the cost-effectiveness will be based on those data, in addition to other data sources like the clinical registration trials.

4.6.3.1 Extramural treatment

In order to be included in the Medicine Reimbursement System (GVS), by which extramural drugs are reimbursed, the manufacturer must formally request a submission for reimbursement at the Ministry of Health. The HCIB will subsequently perform the assessment and appraisal based on the submitted dossier by the manufacturer. The director of the HCIB (or the Board of the HCIB) will give a motivated advice to the Minister of Health regarding reimbursement of the drug in the reimbursement system and on what list the drug should be placed. The reimbursement system contains a positive list of all reimbursed drugs. List IA consists of groups of medical products that are interchangeable, for each group a reimbursement limit exists (reference price system). List IB consists of unique medical products; no reimbursement limit exists for those medical products although prices are restricted due to the Act on Medicine prices (the price of the drug in neighbouring countries is taken as a reference). Both for drugs listed on list IA and for those listed on list IB special conditions for reimbursement may exist; these are listed on list 2. For example the drug is only reimbursed for a small group of patients, or must be prescribed by a specialist.

Next to the reimbursement conditions on List 2 health care insurance companies may also give restrictions, e.g. that the medicine may only be prescribed by a specialist or a specific prescriber (e.g. a specialist with experience in a particular disease).

Based on the EU transparency regulation, the assessment and appraisal procedure followed by the decision of the Minister of Health may last 90 days. In practice, these time lines are in general met for drugs listed on list IA, the ones listed on list IB may take longer especially when special conditions (list 32) are involved. An ongoing assessment procedure can be suspended for three months on request of the MAH in case time is needed to collect necessary information for the assessment of the drug.

The procedure is the same for orphan and non-orphan drugs. The evaluation procedure is done by the Committee for Pharmaceutical Aid (CPA) of the HCIB and is composed of three parts corresponding to the three components of the application file: the pharmacotherapeutic (therapeutic value) evidence, the pharmaco-economic evaluation (cost-effectiveness) and the budget impact provided by the MAH. The CPA will first assess if the drug is interchangeable or not (this means that an alternative is available). If yes, the drug will be included on List IA. If not interchangeable, the CPA judges the therapeutically added value and the cost-effectiveness of the product. It will therefore look at the added therapeutic value (assessing the pharmatherapeutic evidence), the cost-effectiveness (assessing the pharmaco-economic evaluation) and the budget impact^{kk}. If these criteria are met, the product can be included on List IB.^{79 80}

If the indication is a rare disease and no alternative treatment as is the case for most orphan drugs, the MAH may ask for dispensation of the pharmaco-economic evaluation. This request is judged by the HCIB and is frequently given. A dispensation may also be asked for drugs that have a low budget impact (€500,000 annually).

kk The budget impact takes into account (among other things): the number of patients; possible new alternatives; the drug's market share; the possible off-label use; and applicable costs.

4.6.3.2 *Intramural treatment*

Due to limiting hospital budgets equal access to medicines became hampered, especially for the treatment of certain cancers. To overcome the postcode prescription additional funding is provided through the following policy measures:^{ll}

- Policy measure “Expensive drugs” for hospitals: 80% reimbursement if purchase costs of a specific^{mmm} orphan drug account for more than 0.5% of the total drug cost of all hospitals on a macro level.
- Policy measure “Orphan drugs” for academic hospitals: if the orphan drug costs account for more than 5% of the hospital’s drug budget, the surplus will be fully reimbursed to the hospital.

These policy measures provide provisional funding for three years (temporary listing) and require collection of more evidence on the clinical and cost effectiveness of drugs fitting in either group through outcomes research. After maximum three years, the HCIB re-appraises the evidence that has been developed as a result of the additional studies, and on this basis it reviews its decisions on the product listing. When the evidence meets the expectations the drug will be kept on the list (definitive listing). This research fosters the development of expertise for specific rare diseases: a special research programme at ZonMw has been dedicated to fund research on effectiveness of expensive (innovative) drugs and expensive orphan drugs and research on development of methodology for Health Technology Assessments. Funding of the first projects in this research programme has started in 2008, so there are no results as yet.⁷⁴

In 2005, a new instrument for performance-oriented costing system for hospital care and for medical mental health care was introduced for hospital treatments, the Diagnosis and Treatment Combinations (DTC). A DTC includes all the activities and actions performed by the hospital and medical specialist in response to the patient’s need for care. Within a DTC, hospital output prices are determined based on actual production costs. The DTC costs are reimbursed by the patient’s insurance company. For rare diseases there are not many diagnosis and treatment combinations and therefore, in many cases, hospitals are responsible for identifying and funding (from their budget) the treatments outside the DTC provided to patients.⁷⁴

4.6.3.3 *Current situation*

Of the 47 orphan drugs having received a Marketing Authorisation of the EMEA:

- Eight orphan drugs are financed under the “Orphan Drugs” policy rule and one drug has applied for this;
- One orphan drug is financed under the “Expensive drugs” policy rule;
- Five orphan drugs are included on List IA (reimbursement with conditions);
- Eighteen orphan drugs are included on List IB (100% reimbursement);
- Eight orphan drugs are available, but not reimbursed;
- Three orphan drugs still have to apply for reimbursement or are ongoing.

This means that of the 47 EMEA orphan drugs, only three are not available in the Netherlands.

^{ll} These policy rules have been developed in order to ensure equal access of drugs to patients across hospitals in the Netherlands.

^{mmm} Most orphan drugs apply for the policy measure for orphan drugs in order to obtain full funding. It is possible to apply for the policy measure on expensive drugs.

4.6.4 Pricing

There are two mechanisms to regulate the price of drugs. The price of orphan drugs is regulated in the same way as non-orphan drugs.

One mechanism is the incorporation of drugs in the Medicine Reimbursement system in case of extramural treatment. Specific clusters of drugs that are assumed to be therapeutically equivalent are listed on the so-called List IA. A maximum level of financing is established for each cluster on the List A. List IB products are drugs used for extramural treatment that do not have a therapeutically equivalent and do not have a maximum level of price. Until now most orphan drugs that are used for extramural treatment are on List IB. The price is in this case considered together with the reimbursement decision.

The second mechanism is the Regulation on maximum prices of medicinal products that fixes the maximum price that a manufacturer can ask for a medicinal product (listed in List IA). The average prices (ex-factory prices) of Belgium, UK, Germany and France are used to calculate the maximum price scheme. A maximum price is set for each product with a given active substance, strength and formulation (constituting clusters of products).⁷⁴

A price revision takes place every six months according to a basket of prices from Belgium, UK, Germany and France. The inclusion of UK influences the basket because of the value of the pound. This mechanism does not apply to the majority of orphan drugs as they fall under list IB.

The Regulation on maximum prices holds also for those medicinal products that are used for treatments within hospitals and that are either also used extramural treatment or are placed on the policy rule on Expensive medicines or on the policy rule of Orphan drugs.

4.6.5 Distribution

Orphan drugs are distributed through hospital and community pharmacies.

4.6.6 Prescribing

The first prescription will be issued by the specialist physician or general practitioner. Different reimbursement procedures apply whether the drug is prescribed for home treatment (extramural) or is administered within the hospital setting (intramural).

Home treatment costs are reimbursement by the Medicines Reimbursement System. The reimbursement level depends of whether the drugs are included on list IA or on list IB. Drugs listed on list IB are 100% reimbursed, while there is a maximum reimbursement for each cluster of interchangeable products on list IA. The patient will have to pay the surplus above the maximum reimbursement.

Hospital treatment costs are (partly) taken in charge by the hospital's budget.

In case of off label use, reimbursement is automatic for a disease with prevalence less than 1:150,000 inhabitants.

In some cases restrictions are imposed on the reimbursement of orphan drugs. The reimbursement conditions to be found in list 2 of the Law Care Assurance are a first type of restriction. A condition can be that the drug is only reimbursed for a specific indication, making it unavailable for off-label use. For example, miglustat can only be reimbursed if the patient has Gaucher type I and he or she can not be treated with imiglucerase. A second type of restriction is imposed by the health care insurance companies. For example, the medicine can only be prescribed by a specialist or a specific prescriber.⁷⁴

Key points

- The Netherlands have in place policy measures and research incentives on rare diseases/orphan drugs. There are non-official centres of reference.
- Orphan drugs are registered through the EMEA centralised procedure only. Specific legislation governs compassionate use and off-label use of orphan drugs.
- There are several mechanisms to fix prices of orphan drugs.
- The reimbursement procedure considers budget impact and sometimes cost-effectiveness. Often, dispensation for economic evaluation is given. Orphan drugs are fully or partially reimbursed by social insurance.
- Orphan drugs are distributed through hospital and community pharmacies.
- The orphan drug is prescribed by a specialist physician or a general practitioner. Conditions can be applied to the prescription of orphan drugs.
- In the Netherlands, hospitals may apply for full additional funding for orphan drugs that are prescribed within their institution through the policy measure. The additional temporally funding considers therapeutic value, cost prognosis and outcomes research – treatment of all patients need to be documented in a patient registry. After three years definitive listing considers: therapeutic value, budget impact, cost-effectiveness and efficient prescription. The appraisal will be based on these assessment criteria. There is no official threshold for the cost-effectiveness, a range is in place, the acceptable cost/QALY value will be balanced with other criteria depending on the individual case. In case of orphan drugs the therapeutic value, the severity of the disease and the efficient prescription will be important for the decision on definitive listing/ funding.

4.7 SWEDENⁿⁿ

4.7.1 Institutional context

The institution in charge of providing information on rare diseases is the Swedish National Centre for Rare Diseases.

Reimbursement decisions are taken by the Dental and Pharmaceutical Benefits Board (DPBB), a governmental agency deciding whether or not a dental or pharmaceutical product will be subsidised by the State.⁸¹

There are specialised centres for rare diseases in each county (on a regional level) concentrating on clinical care, diagnosis and treatment.⁶⁰

The Swedish National Board of Health and Welfare applies its own definition of a rare disease: “a disorder causing substantial disability and affecting fewer than 100 individuals per million population”.⁹

There is no policy for orphan drugs and there is no specific market access procedure for orphan drugs.

4.7.2 Marketing Authorisation

Orphan drugs obtain Marketing Authorisation through the centralised procedure at EMEA (see previous chapter).

ⁿⁿ This chapter has been reviewed by Mr Karl Arnberg from the Dental and Pharmaceutical Benefits Board

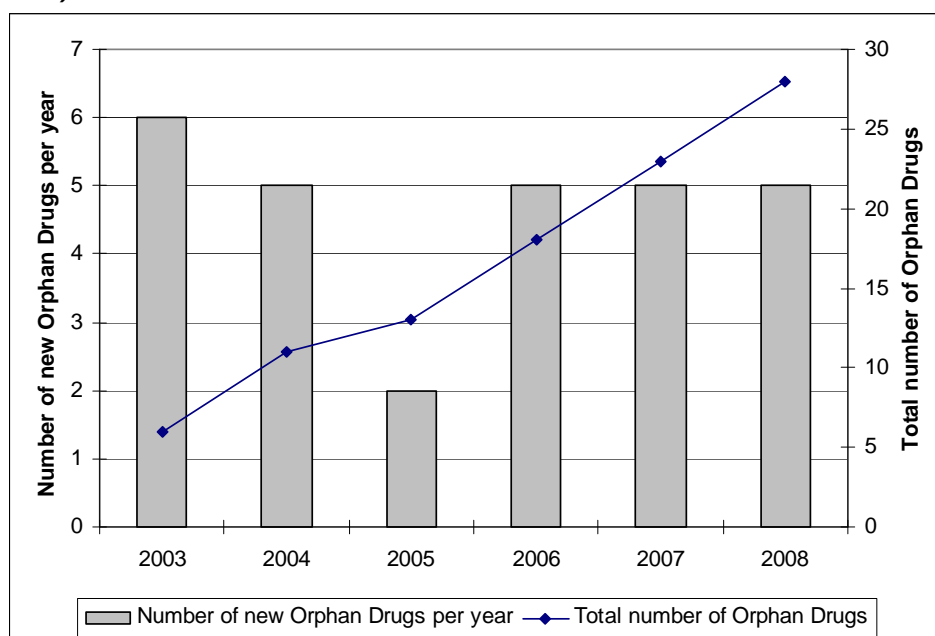
4.7.3 Reimbursement

The DPBB takes reimbursement decisions within a 180-day assessment period. The criteria are the same for orphan and non-orphan drugs being the cost-effectiveness of the product, the human value principle and the need and solidarity principle. The evidence asked is mostly the same clinical data as for the EMEA Marketing Authorisation procedure. Sometimes additional data is requested.⁸²

The cost-effectiveness comprises a comparison of indirect and direct costs with the MAH's health economics analysis. The human value principle implies equality of all persons and the need and solidarity principle implies that products that treat those with the greatest health needs take precedence. Even though cost-effectiveness is important for non-orphan drugs, the human value principle will prevail for both orphan and non-orphan drugs.⁸³ Cost-effectiveness must be proven, but as the threshold is higher for more severe diseases, a greater uncertainty is accepted if there is no possible way of acquiring data (e.g. due to a small patient group).⁸⁴

The approved product is included on the List of Substitutable Products.

Figure 4.13: Number of EMEA orphan drugs reimbursed in Sweden (2003-2008)



Source: Dental and Pharmaceutical Benefits Agency. Medicinal Products Database. <<http://www.tlv.se/beslut/sok-i-databasen/>>. Accessed 28/4/2009.

4.7.4 Pricing

The MAH is able to set the price freely, which will be approved by the DPBB following the abovementioned procedure. If accepted, the product will be included on the positive list of reimbursement. Medicinal products can also be sold without being included on the positive list, but patients will have to pay the full cost. This does not apply to products administered through hospitals: their price is the result of a negotiation between the MAH and the county councils.⁸³

There is no price revision procedure: if a MAH wants to increase the price, the product will first have to be removed from the positive list and a new request will have to be introduced at the DPBB (substitution system). Or in order for the DPBB to approve a price increase for drugs not included in the substitution system, two conditions need to be fulfilled:⁸⁵

1. The medicine in the application is an urgent therapeutic alternative as it is used to treat serious conditions which threaten the patient's life and health. There are patients who risk being without similar treatment if the medicine disappears from the Swedish market.
2. There is a considerable risk that the medicine will disappear from the Swedish market (or that the supply will decrease sharply), if the price increase is not approved.

If the two conditions are fulfilled, the MAH will not have to withdraw from the positive list.

4.7.5 Distribution

Orphan drugs are available through hospital and community pharmacies.

4.7.6 Prescribing

The first prescription can be issued by the specialist physician or the general practitioner, but most patients are treated by a specialist. There are no conditions for prescribing orphan drugs and there is no control mechanism. Reimbursement decisions do not differ between individuals.⁸⁴ Conditions on reimbursement can be imposed, but there are no general conditions specific for orphan drugs.

The level of reimbursement is the same for all types of drugs. Up to 900 SEK (€ 81)⁸⁶ of accumulated total cost of prescribed drugs the patient will bear the full cost. Between 900 and 4,300 SEK the patient will pay a part of the costs and will receive the drugs free of charge once the accumulated total drugs cost has exceeded 4,300 SEK. An overview of the share of patient co-payment is given in the table 4.15.⁸³

Figure 4.14: Patient co-payments in function of the accumulated total costs of prescribed drugs over 12 months in Sweden

Accumulated total costs of prescribed drugs over 12 months	Patient co-payment	Maximum accumulated patient outlay over 12 months
≤ 900 SEK	100%	900 SEK
901 – 1,700 SEK	50%	1,300 SEK
1,701 – 3,300 SEK	25%	1,700 SEK
3,301 – 4,300 SEK	10%	1,800 SEK
≥ 4,300 SEK	0%	1,800 SEK

Reimbursement is done by the Public Social Insurance.

⁸⁶ 1€ = 11,11SEK (20/4/2009)

Key points

- Sweden has in place specific centres of reference, but no policy measures and no research incentives on rare diseases/orphan drugs.
- Orphan drugs are registered through the EMEA centralised procedure only. There is no legislation governing compassionate use or off-label use of orphan drugs.
- There is free pricing of orphan drugs through a system of public procurement at the level of county councils.
- The reimbursement procedure considers cost-effectiveness, but not budget impact because decisions are taken at the country level. Orphan drugs are fully reimbursed by social insurance.
- Orphan drugs are available through hospital and community pharmacies.
- The orphan drug is prescribed by a specialist physician or a general practitioner. No conditions are applied to the prescription of orphan drugs.

4.8 UNITED KINGDOM^{PP}

4.8.1 Institutional context

There is no specific funding for promoting the development of orphan drugs as these take place at a European level. Research projects to fund research networks for rare diseases were not identified.

A distinction has to be made between the regulatory processes, pricing, HTA processes and the commissioning policies:

- Regulatory processes: the medicine obtains a licence at EMEA level;
- Pricing which is regulated by the Pharmaceutical Price Regulation Scheme (PPRS)⁸⁶;
- HTA processes: Three HTA regional bodies provide guidance to the National Health Service on the use of health technologies based on appraisal of clinical and cost effectiveness evidence.⁵⁷:
 - National Institute for Health and Clinical Excellence (NICE) for England. NICE produces guidance on public health, health technologies selected by the health ministers and clinical practice;
 - Scottish Medicines Consortium (SMC) for Scotland which reviews all new medicines. SMC has developed a specific policy for orphan drugs;
 - All Wales Medicines Strategy Group (AWMSG) for Wales issues recommendations on drugs that have not been evaluated by NICE;
- Commissioning: Commissioning in the National Health Service (NHS) is the process by which it is ensured that the health and care services provided most effectively meet the needs of the population⁹⁹.

The cost effectiveness threshold used by NICE to make recommendations on the most appropriate use of medicines within the NHS is also applicable to orphan drugs. Following thresholds are applied: Below a most plausible ICER of £20,000/QALY, judgments about the acceptability of a technology as an effective use of NHS resources are based primarily on the cost-effectiveness estimate (point A in figure 4.15).

^{PP} This chapter has been reviewed by Ms Martina Garau of the Office of Health Economics; it describes mainly the situation in England, unless mentioned differently in the text.

⁹⁹ The National Commissioning Group (NCG) also has a top slice budget for therapies for very rare conditions. See also below.

Above a most plausible ICER of £20,000/QALY, judgments about the acceptability of the technology as an effective use of NHS resources are more likely to make more explicit reference to factors including:

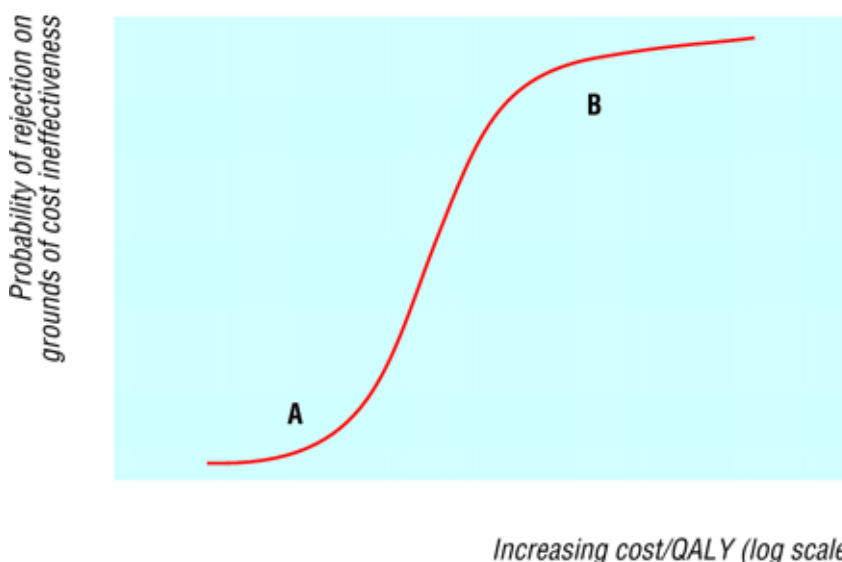
- the degree of uncertainty surrounding the calculation of ICERs
- the innovative nature of the technology
- the particular features of the condition and population receiving the technology
- where appropriate, the wider societal costs and benefits.

Above an ICER of £30,000/QALY, the case for supporting the technology on these factors has to be increasingly strong.(point B in figure 4.15) The reasoning for the Committee’s decision will be explained, with reference to the factors that have been taken into account”.^{87 88}

ICER stands for incremental cost-effectiveness ratio being the extra cost that is paid for each extra unit of health improvement gained by using the medicine, compared to the next most effective alternative. The ICER is measured in terms of the cost per QALY gained (quality-adjusted life year) by the intervention. A QALY gained is a year of life in good health a person might gain as a result of treatment.

Medicinal products with an ICER higher than 30,000£ per QALY are usually not considered as cost effective. For a drug to be cost effective, it must deliver an additional QALY over and above treatments already available. Exceptions have been made for orphan drugs: for example Imatinib for the treatment of myeloid leukaemia was approved at a cost of 48,000£ per QALY (being the highest cost ever accepted).⁸⁹ In January 2009, NICE published a supplementary advice indicating that life-extending medicines for end of life conditions affecting small populations can be recommended by NICE even when they exceed the cost-effectiveness threshold of £30,000/QALY.⁸⁷ This advice will influence decisions on treatments for rare cancers as they fall under end of life conditions, but not long-term chronic rare conditions.⁵⁷

Figure 4.15: Incremental cost per QALY gained (ICER)



Source: Rawlins MD, Culyer AJ. National Institute for Clinical Excellence and its value judgments. *BMJ* (Clinical research ed). 2004(329):224-7.

A debate has been going on for some years on how to define orphan and ultra-orphan drugs. Recently, the Health Minister stated that there is no formal classification of “ultra-orphan” drugs. The term has been used by NICE to indicate treatments for conditions with a prevalence of less than one in 50,000 in the United Kingdom.

The National Commissioning Group (NCG) of the NHS selects diseases with less than 400 cases. Its role is to commission services for the population of England for a specific group of extremely rare conditions, which can include orphan drugs.⁹⁰

4.8.2 Marketing Authorisation

Orphan drugs obtain Marketing Authorisation through the centralised procedure at EMEA (see previous chapter).

The body responsible for regulatory approval in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA) which has not been involved with orphan drug Marketing Authorisation, to date.

4.8.2.1 *Compassionate use*

Prescription of unlicensed drugs is accepted if three conditions are fulfilled:⁹¹

- It is a bona fide unsolicited order;
- The product is formulated in accordance with the requirement of a doctor or dentist registered in the UK;
- The product is for use by individual patients on their direct personal responsibility.

There is not a specific procedure for compassionate use in the UK.

4.8.2.2 *Off-label use*

Off-label use is defined as the use of a licensed medicine for an unlicensed indication or administered via a different route. The medicine will be reimbursed if it is not particularly expensive. Otherwise, the reimbursement and the provision are monitored more strictly. The authority which monitors this is the Prescription Price Authority.⁵⁸

4.8.3 Reimbursement

4.8.3.1 *Uptake of medicine on the market*

The UK has no system of reimbursement similar to the ones in other European countries as medicines are made available after launch and can in principle be prescribed by clinicians operating within the NHS as soon as the Marketing Authorisation is obtained. In practice, there are however mechanisms to control expenditure and a medicine can be appraised by one of the Health Technology Assessment (HTA) bodies (NICE, AWMSG, SMC), which issues guidance on its appropriate use within the NHS. The HTA body makes recommendations to the NHS about which drugs and treatments should be available.

NICE evaluates orphan drugs using the same methods and decision criteria as for all technology appraisals, but a lower level of evidence may be accepted for orphan drugs.⁹²

If NICE rejects a medicine, than the NHS clinicians cannot prescribe it. Technology appraisal consists of three steps:⁹³

1. Scoping: what will be examined;
2. Assessment of clinical and cost effectiveness: by means of a review of evidence and an economic evaluation (cost per QALY) conducted by an academic centre and the manufacturer/s.
3. Appraisal of the assessment taking into account the opinion of consulters, commentators, clinical specialists and patient experts.

While NICE assesses both old and new technologies, the SMC issues guidance on all newly licensed medicines, new indications and formulations.⁹⁴ The AWMSG “appraises new high cost, cardiac and cancer medicines for which no NICE guidance is expected for at least twelve months”.⁹⁵

The SMC has adopted a policy on orphan drugs according to which orphan drugs are appraised in the same way as normal drugs, but modifiers are considered.⁹⁶

These modifiers are additional factors considered when orphan drugs are appraised, such as whether the drug:

- treats a life threatening disease;
- substantially increases life expectancy and/or quality of life;
- can reverse, rather than stabilise, the condition;
- or bridges a gap to a “definitive” therapy.⁹⁷

The AWMSG’s criteria for ultra-orphan drugs are:⁹⁸

- Degree of severity of the untreated disease, in terms of quality of life and survival;
- Whether the drug can reverse, rather than stabilise the condition;
- Overall budget impact;
- Whether the drug may bridge a gap to a “definitive” therapy which is currently in development;
- The innovative nature of the drug.

The assessment of the drugs takes into account the cost-effectiveness based on the price decided by the MAH⁶³

As of April 2008, NICE had appraised only one EMEA-designated orphan drugs, which is imatinib for the treatment of gastro-intestinal stromal tumours and of chronic myeloid leukaemia. In both cases, the treatment was recommended for use.⁹⁹

On the other hand, SMC had reviewed 28 orphan drugs. “Almost half of them were rejected (13), 12 were recommended and three were recommended for restricted use, i.e. for patient sub-group/s within the licensed indication”.⁹⁹

The price of medicines funded by the NHS is included in a national list of tariffs, the British National Formulary (BNF). Funding takes place through the budget of the National Health Service.

4.8.3.2 Commissioning

England, Wales and Scotland have each developed specific funding mechanisms for orphan drugs, which are broadly similar. In England, health care services, including medicines, for very rare diseases are commissioned by the NCG. The NCG will assess diseases with an incidence of less than 400 cases.⁴⁴ On a regional level, services can be referred to the Specialised Commissioning Groups.

The commissioning consists of an assessment of the health service needs and the current service provision for the local population. Based on this assessment, the Primary Care Trusts (PCTs) at local level identify what type and level of services need to be procured in the coming year from primary care services providers, such as General Practitioners or pharmacists, or from secondary care institutions, such as hospitals and mental health trusts.⁵⁵ The PCTs are responsible for the funding.

4.8.4 Pricing

The pricing mechanism is the same for orphan and non-orphan drugs.

Prices are set freely by the MAHs, but have to meet the profit control criteria included in the PPRS. This scheme is an agreement between the Department of Health and the Association of the British Pharmaceutical Industry.⁸⁶

There are two mechanisms for price revisions:

- “flexible pricing where a price decrease or increase by the MAH is possible if there is new evidence or if a different indication is being developed (the flexible pricing mechanism will allow to have prices which better reflect the drug therapeutic value);
- patient access schemes: early access to medicines which are not in first instance found to be cost and clinically effective by NICE”.¹⁰⁰

According to the 2009 PPRS agreement, MAHs are able to modulate the list price of their PPRS products by changes that equate to an overall level of 3.9% in 2009.

Price revisions take place on an infrequent basis.

4.8.5 Distribution

Orphan drugs are distributed through hospital pharmacies and specialist centres.

4.8.6 Prescribing

The first prescription will be issued by the specialist physician. The prescription has to be consistent with the license.

The prescription process is influenced, and therefore controlled, by the guidance, when available, of the HTA bodies on the use of medicines within the NHS.

Differences in individual HTA decisions occur on a regional level as medicines are appraised by different HTA bodies (NICE, SMC and AWMSG) who can take different decisions.

Key points

- **There are no policy measures and research incentives on rare diseases/orphan drugs in the UK. There are specific centres of reference for some orphan drugs.**
- **Orphan drugs are registered through the EMEA centralised procedure only. Specific legislation governs compassionate use and off-label use of orphan drugs.**
- **Prices are set freely by the MAHs, but have to meet profit control criteria.**
- **Orphan drugs are either fully or not reimbursed**
- **The reimbursement procedure considers budget impact and cost-effectiveness. Orphan drugs are fully reimbursed by the National Health Service.**
- **Orphan drugs are available through hospital pharmacies.**
- **Orphan drugs are prescribed by specialist physicians. The prescription process is influenced by the guidance of HTA bodies, if available.**

4.9 COMPARATIVE ANALYSIS

Regulatory traits of the rare disease and orphan drug market in the six countries studied are presented in Figure 4.16.

With respect to the institutional context, France, Italy, Sweden and (partly) the UK have dedicated centres of reference for orphan drugs and rare diseases. University medical centres fulfil this role in the Netherlands. A similar situation applies for Belgium as mentioned above with four networks of centres that can be considered to partially fulfil the role of centres of reference. In addition to European measures to promote research and development of orphan drugs, France, Italy and the Netherlands have implemented additional policy measures and research incentives for orphan drugs and rare diseases.

Orphan drugs are registered through the EMEA centralised procedure in all six countries. Countries have introduced specific legislation governing compassionate use of orphan drugs, except for Sweden. Italy, the Netherlands and the UK have implemented a procedure for off-label use of orphan drugs.

Prices of orphan drugs are subject to price fixing in all countries, except for Sweden (at the county level) and the UK. In France, Italy and the Netherlands, prices are fixed with reference to, amongst other things, the price level in other EU countries. In the Netherlands, maximum prices are fixed for orphan drugs. In order to maximize price competition, prices in Sweden are determined by a system of public procurement at the regional level. In the UK, orphan drug prices are set freely by the MAHs, but have to meet the profit control criteria.

To gain reimbursement, formal cost-effectiveness analysis is sometimes but not always performed for orphan drugs in the countries studied. The budget impact of orphan drugs is considered in the reimbursement application in all countries, except for Sweden. Orphan drugs are not always fully reimbursed in all countries studied. Orphan drugs are fully reimbursed in Italy, Sweden, Belgium and the UK. France and the Netherlands operate a mixed system of full or partial reimbursement.

Orphan drugs are distributed through hospital pharmacies in all countries studied. Additionally, they are distributed through community pharmacies in Italy, France, the Netherlands, and Sweden; they are also distributed through health authorities in Italy; and through specialist centres in the UK.

Orphan drugs are initially prescribed by a specialist physician or a general practitioner in the Netherlands and Sweden. The prescription is the exclusive responsibility of the specialist physician in Belgium, Italy and the UK. All countries studied impose conditions on prescribing orphan drugs, except for Sweden. In Italy, if an orphan drug is prescribed to a patient, the treatment must be registered in a national registry. Delivery of the drugs depends on provision of the data for the registration. This is also partly the case in Belgium for orphan drugs for which a CMDOD exists. In France, orphan drugs are reimbursed only if the rare disease is one of the indications. In the Netherlands, health insurance funds have the right to impose additional prescribing conditions. In the UK, the prescription process of orphan drugs is influenced by the guidance of HTA bodies, if available.

The number of available orphan drugs per country varies:

Belgium	31 orphan drugs reimbursed, 2 not reimbursed but available (2008) ^{rr}
France	35 orphan drugs (2007)
Italy	23 molecules (2007)
The Netherlands	44 orphan drugs of which 36 are reimbursed (2008)
Sweden	28 orphan drugs
United Kingdom	Information not available. All are in theory available, but not all are reimbursed.

The highest availability of orphan drugs is achieved in the Netherlands and France.

^{rr} See table 8.1 in annex for the full overview. Drugs available for compassionate use or available but not yet reimbursed are not included.

Figure 4.16: Regulation governing rare disease and orphan drug markets

Features	Belgium	France	Italy	Netherlands	Sweden	UK
INSTITUTIONAL CONTEXT						
<i>Existence of centres for rare diseases/orphan drugs:</i>	No	Yes	Yes	No	Yes	Yes
<i>Policy measures to promote development of orphan drugs:</i>	No	Yes	Yes	Yes	No	No
<i>Incentives for research on rare diseases/orphan drugs:</i>	No	Yes	Yes	Yes	No	No
MARKETING AUTHORISATION						
<i>Existence of national Marketing Authorisation procedure:</i>	No	No	No	No	No	No
<i>Procedure for compassionate use of orphan drugs:</i>	Yes	Yes	Yes	Yes	No	Yes
<i>Procedure for off-label use of orphan drugs:</i>	No	No	Yes	Yes	No	Yes
PRICING						
<i>Pricing system:</i>						
- Free market					Yes (county level)	Yes
- Price fixing	Yes	Yes	Yes	Yes	Yes (national level)	
REIMBURSEMENT						
<i>Third-party payer:</i>						
- National Health Service			Yes			Yes
- Social insurance	Yes	Yes		Yes	Yes	
<i>Reimbursement based on cost-effectiveness:</i>	No	Yes	Yes	Sometimes	Yes	Sometimes
<i>Reimbursement based on budget impact:</i>	Yes	Yes	Yes	Yes	No	Yes
<i>Reimbursement level:</i>						
- Full reimbursement	Yes	Yes	Yes	Yes	Yes	Yes
- Partial reimbursement	No	Yes		Yes		
DISTRIBUTION CHANNELS						
<i>Delivery channels:</i>						
- Hospital pharmacies	Yes		Yes	Yes	Yes	Yes

Features	Belgium	France	Italy	Netherlands	Sweden	UK
- Community pharmacies			Yes	Yes	Yes	
- Health authorities			Yes			
- Internet						
- Other						
PRESCRIBING PROCESS						
<i>Prescription by:</i>						
- Specialist physician	Yes		Yes	Yes	Yes	Yes
- Nurse practitioner				Yes	Yes	
- General practitioner				Yes	No	
<i>Existence of conditions for prescribing orphan drugs:</i>	Yes	Yes	Yes	Yes	No	Yes

5 CRITICAL ASSESSMENT

5.1 INTRODUCTION

Chapter 4 has described the reimbursement procedure for orphan drugs in Belgium. Since 2002, the Drug Reimbursement Committee (DRC) of the NIHDI (National Institute for Health and Disability Insurance), the Belgian third-party payer, evaluates drug reimbursement requests based on multiple criteria: the therapeutic value, price and proposed reimbursement tariff, the importance of the drug in clinical practice, and the budget impact of the drug. No economic evaluation of the orphan drug is required for reimbursement purposes.

The aim of this chapter is to carry out a critical assessment of reimbursement request files of orphan drugs that have been submitted in Belgium since end 2001, the date that the new reimbursement procedure (not specific to orphan drugs) came into effect^{ss}. First, a qualitative overview was conducted of the reimbursement dossiers of all orphan drugs focusing on the evidence submitted for each reimbursement criterion. Second, a number of orphan drugs were selected for an in-depth analysis. A critical assessment provided in the context of a drug reimbursement request for these orphan drugs was conducted and compared with the assessment report of the DRC (see point 5.4.2).

Key points

- **This chapter conducts a qualitative overview of the reimbursement files of all Belgian orphan drugs focusing on the evidence submitted for each drug for each reimbursement criterion.**
- **A critical assessment was carried out of the scientific evidence for 8 selected orphan drugs and compared with the assessment report of the DRC.**

5.2 METHODOLOGY

5.2.1 Qualitative overview

The qualitative overview was based on an examination of the reimbursement request files of orphan drugs submitted to the DRC. The following information was extracted from the dossiers: description of the orphan drug; reimbursement status; therapeutic value and needs; budget impact; and number of registered indications. Each drug was identified in terms of its name, code according to the Anatomical Therapeutic Chemical (ATC) drug classification system¹⁰¹ and supplier. The reimbursement status related to whether the dossier was an original application or a revision and whether reimbursement had been awarded. The quality of clinical evidence used to assess the therapeutic value of orphan drugs was evaluated by focusing on the number and design of clinical studies. The analysis also considered whether clinical studies had been published in peer-reviewed journals. The therapeutic needs for an orphan drug were analysed by taking into account its place in clinical practice (first- or second-line treatment) and whether any alternative treatment existed. The budget impact was determined by means of the number of patients and the cost per patient per year as reported in the reimbursement dossiers. Finally, the number of indications was reported for which the orphan drug was registered with the European Medicines Agency (EMA) and for which the orphan drug sought reimbursement in Belgium.

Companies need to submit a revised dossier to the DRC after 1.5 to 3 years following initial reimbursement approval (see chapter 4). Our analysis covered the finalised dossiers relating to the revised application of three orphan drugs, whose reimbursement was initially granted in 2004 and the initial application of 23 orphan drugs.

ss KB 21/12/2001 tot vaststelling van de procedures, termijnen en voorwaarden inzake de tegemoetkoming van de verplichte verzekering voor geneeskundige verzorging en uitkeringen in de kosten van farmaceutische specialiteiten. Belgisch Staatsblad 29/12/2001.

5.2.2 In-depth analysis

Eight orphan drugs were selected for an in-depth analysis. These cases were chosen to reflect the variety of reimbursement applications submitted to the DRC.

5.2.2.1 Criteria for selection

A panel of three experts agreed on the following selection criteria for cases (in descending order of importance):

Criteria level 1:

- Nature of disease: metabolism, oncology, toxicology, endocrinology, cardiovascular, hematology
- Therapeutic value
 - Evidence published: yes/no
 - Number of studies and phase I, 2, 3 or 4
- Is it a first submission or a revision

Criteria level 2:

- Budget impact
 - Prevalence
 - Cost/patient/year

Criteria level 3:

- Supplier
- Therapeutic need
 - 1st or 2nd line treatment
 - Alternative available: yes/no

5.2.2.2 Choice of cases

Applying the criteria and looking for the highest coverage for each criterion resulted in the following selection: *Pedea*®, *Aldurazyme*®, *Fabrazyme*®, *Replagal*®, *Tracleer*®, *Trisenox*®, *Xagrid*®, *Zavesca*®. *Pedea*® was a 'negative' case. The 7 other drugs turned out to be the 'oldest' cases.

Together, these provide for a good spread over the different situations that can occur, over the natures of diseases possible, stand for a significant potential budget impact, and are produced by various different manufacturers.

Figure 5.1 Overview of the eight cases

	<i>Aldurazyme</i> ®	<i>Fabrazyme</i> ®	<i>Replagal</i> ®	<i>Tracleer</i> ®	<i>Trisenox</i> ®	<i>Xagrid</i> ®	<i>Zavesca</i> ®	<i>Pedea</i> ®
Nature of disease	metabolic	metabolic	metabolic	cardiovascular	oncology	hematology	metabolic	cardiovascular
Evidence published	no	yes	yes	no	yes	yes	yes	No
Phase study	1 double-blind RCT	1 double-blind placebo 2x3 1x4	2x2	1x3	1x2	1x1/2	1x1/2	6 RCTs
First or revision	2	2	2	1	1	1	1	1
Budget impact (prevalence / cost per patient per year)	12 / €40 000	50-75 / €200 000	50-75 / €200 000	300 / €39 000	9 / €25 000	11000 / €7 500	90 / €94 000	200-300 / €381
supplier	Genzyme	Genzyme	Shire EGT	Actelion	Cephalon	Shire	Actelion	Orphan Europe
1 st or 2 nd line	1	1	1	1	2	2	2	1
Alternative available	No	Yes, Replagal	Yes, Fabrazyme	Yes	No	Yes	Yes	Yes, Indomethacine

Key points

- **The qualitative overview extracted information about the orphan drug; reimbursement status; therapeutic value and needs; budget impact; and number of registered indications from each reimbursement dossier.**
- **A number of orphan drugs were selected for in-depth analysis. They were selected on the basis of the nature of disease, therapeutic value, reimbursement status, budget impact, supplier and therapeutic needs.**

5.3

QUALITATIVE OVERVIEW OF ALL REIMBURSEMENT DOSSIERS

Between January 2002 and June 2008, reimbursement dossiers of 26 orphan drugs submitted to the DRC have been finalised. Reimbursement has been awarded to the majority of orphan drugs (22 out of 26 drugs). Table 9.2 in annex summarises reimbursement dossiers of all 26 drugs. Some of these have been re-submitted at a later date.

The DRC's advice was positive for 19 drugs. All these were approved by the Minister of Social Affairs.

For one drug, there was no advice from the DRC, as no consensus could be reached. This drug was approved by the Minister of Social Affairs

Two out of the six drugs for which the DRC's advice was negative, were granted reimbursement by the Minister.

For two of these three drugs it appears from the dossiers that both the DRC and the pharmaceutical company proposed a number of elements for negotiation - including a price decrease, employment opportunities, restrictions on the size of the patient population, the funding of diagnostic tests by the company, a reduction of the dosage - which may have played a role in awarding reimbursement.

In the case of the third orphan drug, EMEA had granted an initial conditional marketing authorisation subject to the condition that the pharmaceutical company carried out additional clinical studies and submitted a new registration application to EMEA. In Belgium, reimbursement was granted to this drug, even though the DRC noted that there was insufficient evidence of the effectiveness of the drug in daily clinical practice and in the long-term. Following a new registration application, the DRC will revisit the reimbursement application. The provisional award of reimbursement in return for an engagement to undertake further clinical research amounts to a public subsidy for clinical research. It could be argued that this creates an uneven playing field for clinical research between pharmaceutical companies.

The rationale for not granting reimbursement to four orphan drugs may be related to the high cost of the orphan drug in comparison with alternative drugs or the existence of other non-orphan indications of the drug.

Using the first level of the ATC drug classification system, orphan drugs mainly related to 'L Antineoplastic and immunomodulating agents' (10 drugs) and 'A Alimentary tract and metabolism' (9 drugs); but also included 'C Cardiovascular system' (2 drugs); 'V Various' (2 drugs); 'G Genitor-urinary system and sex hormones' (1 drug); 'H Systemic hormonal preparations, excluding sex hormones and insulins' (1 drug); and 'N Nervous system' (1 drug).

The evidence of therapeutic value included in the reimbursement dossier was similar to the evidence submitted to EMEA for registration purposes. This may reflect the short time period (an average of 130 days according to NIHDI/INAMI data) between EMEA registration approval and submission of the reimbursement application to the DRC in Belgium. The reimbursement dossier of one orphan drug included an additional clinical study that had not been available at the time of registration with EMEA.

In general, the evidence of therapeutic value was limited, with evidence derived from few clinical studies.

The methodological design of studies varied considerably, with clinical evidence derived from double-blind randomised controlled trials, open-label studies and case series. Ten dossiers included clinical evidence from double-blind randomised controlled trials for orphan drugs relating to various ATC drug classes including 'A Alimentary tract and metabolism', 'C Cardiovascular system', 'G Genitor-urinary system and sex hormones', 'L Antineoplastic and immunomodulating agents' and 'G Genitor-urinary system and sex hormones'. Clinical studies of 13 orphan drugs had been published in peer-reviewed journals.

Orphan drugs were positioned as first-line treatment (11 drugs) or second-line treatment (10 drugs) or both (4 drugs). There appears to be a therapeutic need for some orphan drugs in the absence of alternative treatments. However, alternative treatments were available for 15 orphan drugs. In this respect, it should be noted that some orphan drugs shared common indications, i.e. Nexavar[®] and Sutent[®] for advanced renal cell carcinoma; Fabrazyme[®] and Replagal[®] for Fabry disease; Revatio[®], Tracleer[®] and Thelin[®] for pulmonary arterial hypertension; Glivec[®], Sprycel[®] and Tasigna[®] for chronic myeloid leukaemia; Ceplene[®], Revlimid[®] and Thalidomide[®] for multiple myeloma.

In the absence of Belgian methodological guidelines to conduct a budget impact analysis, analyses included in reimbursement dossiers were generally simplistic. The number of patients and drug market share in Belgium were estimated or assumed by the pharmaceutical company. Budget impact analyses considered drug reimbursement tariffs rather than public prices. No dossier took into account the fact that the potential reimbursement of the orphan drug is likely to influence the market share of and the number of patients using alternative drugs or treatments. Potential savings are nearly never mentioned. Analyses were limited to examining the impact of drug costs and did not consider total treatment costs. One can assume this is not done as the cost of the drug is dominant in the treatment cost, and other costs like consultations or tests, are marginal in comparison.

In general, reimbursement was sought in Belgium for the indication registered with EMEA. For three drugs, a reimbursement application was submitted for one of two indications registered with EMEA. If a pharmaceutical company submits multiple reimbursement dossiers relating to different indications of the orphan drug rather than one dossier relating to all indications, the DRC assesses the budgetary impact for an individual indication, but is not able to assess the total budgetary impact spanning all indications of the orphan drug.

Key points

- **Reimbursement is awarded to the majority of orphan drugs.**
- **In addition to the official criteria used by the DRC, other arguments such as price, employment, patient population, funding of diagnostic tests by the company may play a role in the reimbursement decision of the Minister.**
- **The provisional award of reimbursement to one orphan drug in return for an engagement to undertake further clinical research in effect amounts to a public subsidy for clinical research.**
- **Decisions of not granting reimbursement to some orphan drugs were related to the high cost of the orphan drug in comparison with alternative drugs or the existence of other non-orphan indications of the drug.**
- **It is possible to derive evidence of therapeutic value from double-blinded randomized controlled trials.**
- **There appears to be a therapeutic need for some orphan drugs in the absence of alternative treatments.**
- **Budget impact analyses were simplistic and there is a need for principles of good practice for budget impact analyses.**

- **The DRC needs to consider the total budget impact of successive reimbursement dossiers of an orphan drug relating to different indications.**

5.4 IN-DEPTH ANALYSIS OF 15 SELECTED REIMBURSEMENT DOSSIERS

5.4.1 Comparison of the evaluations by EMEA

5.4.1.1 *Objective*

One of the objectives of the KCE project was to document the different steps leading to approval and reimbursement of orphan drugs in Belgium. The data on which decisions are based, are provided to EMEA by the company in the form of a Marketing Authorisation application file (Common Technical Dossier, CTD). If regulatory approval is obtained a European Public Assessment Report (EPAR) and the Summary of Product Characteristics (SPC) are made public by EMEA. In order to obtain reimbursement for the approved drug the company provides data to the Belgian agency deciding on reimbursement (NIHDI).

In order to get a feeling for the possible redundancy of the local evaluation it was checked whether the same study data sets were provided to EMEA and NIHDI, and whether the EPAR could be considered an alternative for the local evaluation (and if not how, it could be improved to also serve this purpose).

5.4.1.2 *Methodology*

First, a list of EMEA approved orphan drug indications was compiled based on either cases selected for the KCE study or recent approvals. The approval could be under exceptional circumstances or not. The list is given in annex 8.6.

For each drug we focused on the first EMEA approval of orphan indication(s). We focused on clinical efficacy and only on the primary endpoint. This is a limitation of the study. Evaluating benefits and risks of an orphan drug in a specific indication involves much more than just looking at a primary endpoint. However the primary endpoint has the advantage that the method of analysis is (or should be) pre-defined in the study protocol and the statistical analysis plan of the sponsor.

In case Marketing Authorisation had been granted under exceptional circumstances without study and demonstration of benefit based on clinical endpoints, the CHMP requested phase 4 clinical trial was considered instead, which was performed in order to obtain a normal Marketing Authorisation.

The pivotal clinical efficacy trials were identified and their pre-defined primary endpoint, as well as the result obtained. These steps were followed separately for the three data sources and compared.

1. The Marketing Authorisation application file (common technical document (CTD part 2 (2.7.3), clinical summary which include the clinical summary or expert report, tabular formats, study synopsis (the full ICH study reports were not checked).
2. The European Public Assessment Report (EPAR) and the SPC.
3. The file submitted by the company to the Belgian NIDHI for obtaining reimbursement.

Data sources 1 and 2 were compared first. The CTD part 2.7.3 of the EMEA Marketing Authorisation application file was made available for review during a visit at EMEA in FEB 2009, under confidentiality. The EPAR reflecting the first orphan indication approval was in most cases available from the EMEA website or was made available for review during a visit at EMEA in FEB 2009, under confidentiality.

5.4.1.3 Results for comparison of CTD part 2.7.3 and EPAR

In all of the 15 drug-indication pairs reviewed we identified the same pivotal trials and in most cases no differences were seen for the primary endpoint results between the CTD part 2.7.3 and the EPAR/SPC.

As these are orphan drugs, for the vast majority of the 15 cases there is only a single pivotal trial with clinical endpoints.

In two out of the 15 cases the results of the main statistical test as pre-defined in the study protocol for analysis of the primary endpoint was not mentioned in the EPAR/SPC, but instead only the result of an alternative statistical method was taken forward by the assessors and communicated as a measure of risk reduction. In both cases the effect of treatment using the pre-defined main statistical method was not significant. In both cases the alternative statistical method provided a p-value that was smaller than the prospective analytic method, and was numerically less than 0.05 in one case. The meaning of such alternative analyses is uncertain, given both the post-hoc nature and the multiplicity of analyses. It must be stated that these observations refer to a period in time when no templates were in use for the CHMP assessment report. Structure and level of detail was left to the discretion of the rapporteurs. In 2002, and following a major revision in 2004, the CHMP has adopted new templates for the assessment reports, including detailed guidance and structure in line with internationally agreed standards of scientific publications based on the CONSORT statement (The Lancet 2001; 357: 1191-94). Such templates are currently in use throughout the scientific assessment and have improved the assessment reports.

In case of ongoing trials, the differences between the CTD and the EPAR in results for the primary efficacy variables was explained by additional information (more patients, longer follow-up) which became available at EMEA during that part of the review process which ends with drug approval and publication of the EPAR. This additional information was on file at EMEA but was not available for verification during the EMEA visit. An additional visit for checking these items was not considered necessary by KCE.

In case results of new studies are provided by the applicant after publication of the first EPAR it is not always possible to find the results for the primary endpoint at the EMEA website. This observation is in agreement with EMEA policies: only certain types of variations trigger a revision of the EPAR, such as variations of the therapeutic indication.

5.4.2 Comparison of the studies mentioned in the NIHDI file, the EMEA file and EPAR

A comparison has been made between the primary endpoints of studies mentioned in the NIHDI file (being the company's application sent to NIHDI), the company's application sent to EMEA and the information contained in the EPAR. This comparison was performed for fourteen orphan drugs and fifteen indications.

- In six cases the information provided in all three documents was the same.
- One NIHDI file only contained the main study, not the supportive nor the extension study.
- In two cases, the NIHDI file contains fewer studies than the EMEA file and EPAR. For the first drug, of the two studies contained in the EMEA file and EPAR, the study phase I/II is not mentioned in the NIHDI file. As for the other study, no numbers are given but the explanation is in line with the one of the EPAR. For the second drug, one phase II study with a primary endpoint of $p=0.42$ is not mentioned.
- In one case the two studies of the NIHDI file correspond to the studies in the EMEA file and the EPAR. Nevertheless, the results of the second study are taken from the SPC (Summary of Product Characteristics) produced by EMEA. A negative study listed in the EMEA file is not mentioned in the NIHDI file.

- In one case the NIHDI file does not give figures, but explains the results, corresponding to the figures in the EMEA file and EPAR.
- Two NIHDI files contain one additional study compared to the EMEA file and EPAR. This can be explained by the fact that the study started after or that the study's first results were published after the EMEA procedure ended.
- For one orphan drug, the studies are the same in all documents, but the results differ. This can be due to the fact that the study covered a long time-period and that results were measured at several times.
- In one case the NIHDI file concludes the study showed a positive effect, while the EPAR states that *"the data are too limited to conclude on the appropriate dosing in children"*.

In general, it can be said that the sponsor's application files sent to NIHDI contain similar but not always the same data as the ones provided to EMEA and to be found in the EPAR. Differences are, when they occur, relatively small, although it is observed that if they occur, they are always to the advantage of the product. It is uncertain whether this has had an impact on the reimbursement decisions.

Key points

- **In most cases, no differences were seen between the CTD part 2.7.3. and the EPAR/SPC in terms of primary endpoint results.**
- **In two cases, an alternative statistical method was reported in the EPAR/SPC than the statistical test pre-defined in the study protocol.**
- **In case of ongoing trials, differences between CTD and EPAR could be explained by additional information becoming available during the review process.**
- **Generally, the companies' drug reimbursement request files sent to NIHDI contained similar but not always identical information as the ones provided to EMEA and to be found in the EPAR. Small differences observed were always to the advantage of the product.**

6 BUDGET IMPACT ANALYSIS

6.1 METHODOLOGY

The budget impact analysis of the orphan drugs on the Belgian health care budget is performed based on the situation at the end of 2008.

The analysis is split into two parts:

- an estimate of the budget impact at the end of 2008 in Belgium;
- the development and application of scenarios for the future to estimate budget impacts in the short and medium term.

The estimate at the end of 2008 has been done combining all potential information sources which is described in section 6.2 below. Most of these sources provide partial information which leaves a high level of uncertainty.

Forecasts are based on scenarios that are described in section 6.3. The starting point for these forecasts is the estimate made for 2008.

6.2 BUDGET IMPACT IN BELGIUM AT THE END OF 2008

At the end of 2008, 31 different orphan drugs were approved for reimbursement in Belgium (of which 30 since 2003 when the Belgian orphan drug legislation was implemented). These 31 drugs correspond to 35 different indications.

Figure 6.1 : Number of orphan drugs reimbursed per year in Belgium

Approved in:	
1999	1
2003	1
2004	6
2005	3
2006	2
2007	7
2008	11
Total orphan drugs	31

More than half of the 31 drugs were approved in the last 24 months.

Figure 6.2 : Number of orphan drugs reimbursed per year and total over the years 1999-2008 in Belgium

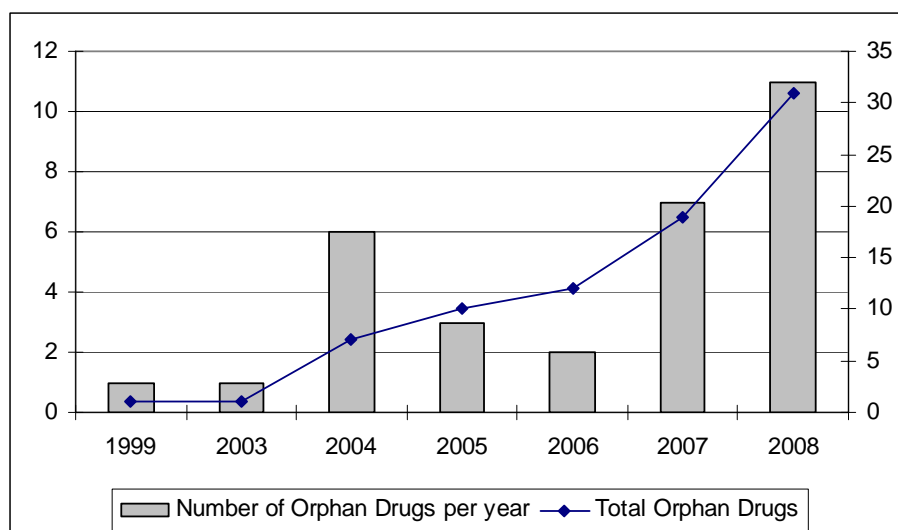


Figure 6.3 provides an estimate of the budget impact for all drugs approved by the end of 2008.

These estimates are tentative, given the high degree of uncertainty of some variables. The reality lies probably in a bracket from -30 % of the calculated estimate to +30 %. For 2008, the real budget impact can therefore be located between 50 and 85 million Euro.

The first source of information is the Ministerial Decree which always includes an estimate of budget impact. This published information¹⁰² is based on the original file submitted by the sponsor to obtain reimbursement. The estimate made by the industry is always reviewed during the approval process, and sometimes a new (different) estimate is made by the DRC.

The estimates provided in the Ministerial Decree are based on assumptions regarding some variables and are thus uncertain:

- The number of patients is unknown, and simply applying the prevalence figures systematically leads to overestimates because not all patients will be treated.
- In most cases, some time is needed to actually identify patients who may use the drug: the uptake of the medicine takes time (a few years).
- Not all patients actually consume the doses as defined by the industry. There can be various reasons for this, but in practice, this will lead to a lower budget impact than forecasted.

Various other sources were used to make the estimate and cross-check:

- Figures published by the NIHDI based on their internal information. These figures were made public at a hearing at the Federal Parliament in February 2009 and are also part of the MORSE report.¹⁰³ These include the number of patients that filed a demand to “colleges” for approval of reimbursement.
- Figures available at the FPS Economy. The FPS Economy is in charge of approving pricing, and collects on a yearly basis the turnover information directly from the industry. The information obtained covered 2007 and was for a relatively small number of drugs.
- Revision files: various drugs had to submit files for revisions, whether as a planned revision for drugs having been more than three years on the market, or because they asked for an extension (e.g. a new dose). These files and the published Ministerial Decrees, include more recent information on the budget impact than was available in the original files.
- Information from the SSF: the SSF is used to obtain reimbursement for individual patients between the Marketing Authorisation and the reimbursement decision by the CTG.
- IMS figures.

All estimates are based on a calculation based on the number of patients (linked to the prevalence) and the average cost of a treatment of a patient. The table below therefore includes the information on prevalence, number of patients and average cost. A scoring was also included as to the reliability of the estimate:

- Score A = both the number of patients and the average cost can be considered as fairly reliable estimates;
- Score B = either the number of patients or the average cost can be considered as highly uncertain;
- Score C = both the number of patients and the average cost can be considered as uncertain.

This estimate should be considered as an operational exercise rather than scientific as it combines different types of information sources: forecasts for the drugs recently launched and real figures for drugs that are longer on the market.

Figure 6.3 : Overview of the estimated budget impact of orphan drugs in Belgium

Orphan drug	Reimbursed since	Nature of disease (O= oncological, NO = not oncological)	Number of Patients treated	Cost/patient / year in 000 €	Total estimated cost to budget 2008 in 000 €	Reliability of estimate
Aldurazyme®	1/8/04	NO	9	312	3,600	A
Atriance®	1/6/08	O	24	23 / adult; 14 / child	160	B
Busilvex®	1/10/08	NO	~44	4.6	205	B
Carbaglu®	1/9/06	NO		14 -1 085	1,106	A
Duodopa®	1/3/07	NO	73	49	4,000	A
Elaprase®	1/1/08	NO	8	300	1,600	B
Evoltra®	1/7/08	O	~10	64	200	C
Exjade®	1/8/07	NO	~1 080	Varies	3,000	B
Fabrazyme®	1/8/04	NO	48	195	7,500	A
Glivec®	As drug cat 2 (1/7/2003)	O	120	31- 48	4,800	A
Increlex®	1/8/08	NO	1	40	40	A
Lysodren®	1/1/08	O	36	6.5	167	C
Myozyme®	1/5/07	NO	23-33	176 / child; 411 / for adult	7,800	B
Naglazyme®	1/12/08	NO	0	376	0	A
Nexavar®	1/4/07	O	215	24 weeks: 15 30 weeks: 19 52 weeks: 33	3,700	B
Orfadin®	1/7/06	NO	14	50 -100	1,200	B
Replagal®	1/8/04	NO	<i>Cost already counted in Fabrazyme</i>			B
Revatio®	1/6/07	NO	70-142	7 - 26	1,500	B
Revlimid®	1/4/08	O		60	5,500	B
Savene®	1/9/07	NO	29	10	150	C
Somavert®	1/4/04	NO	70 per year		1,600	C
Sprycel®	1/9/07	O	85-900		4,800	B
Sutent®	1/4/07	O	GIST: 73 mRCC: 180- 240	GIST: 6 mRCC: 21	3,000	C
Tasigna®	1/9/08	O	<i>Cost counted with Sprycel</i>			B
Thelin®	1/1/08	NO	50	32	3,900	A
Torisel®	1/12/08	O	0	30	0	A
Tracleer®	1/8/04	NO	358	37	4,700	B
Trisenox®	1/11/05	O	4	37	275	A
Xagrid®	1/11/05	NO	320	7	1,500	A
Zavesca®	1/9/05	NO	2	93	200	A
TOTAL					66,203	

Comments regarding this estimated budget impact:

- One orphan drug has not been included because of absence of information (Thalidomide®).
- The estimated cost is only the cost of the drug, not of the total treatment.
- Savings are not taken into account. For orphan drugs in the category “no alternative”, the potential saving is linked to treatment of symptoms of the disease. For orphan drugs in the category “significant benefit”, the saving is the alternative treatment.
- The costs of the orphan drugs reimbursed through the SSF are not included in the table above, as they are not yet known for 2008 and cover orphan drugs that are not part of the “official list” of reimbursed drugs. (The SSF reimbursing only drugs not (yet) reimbursed under the normal scheme). For 2007, this cost was near to € 4 million, but one drug (Myozyme®) accounted for € 3.5 million.

The total estimated cost to the NIHDI budget of € 66.2 million corresponds to more than 5 % of total hospital drugs budgets in 2008.

6.3 BUDGET IMPACT FORECAST

Three scenarios are applied to estimate the future budget impact: a conservative scenario (low growth/cost), a realistic scenario (best estimate) and a higher growth/cost scenario.

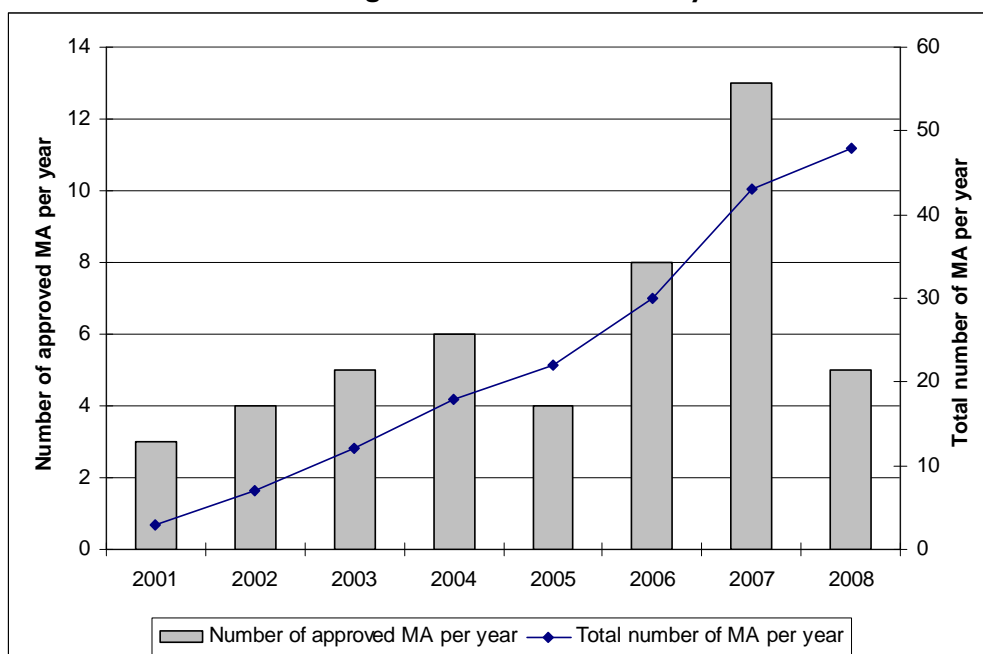
These scenarios are based on following variables:

- An estimate of the average number per year of orphan drugs that will obtain a Marketing Authorisation at the European level.
- An estimate of the number of drugs per year that will obtain a positive reimbursement decision in Belgium.
- The average cost per patient per year per drug.

The applied estimate of the average number of orphan drugs that obtain a Marketing Authorisation is based on the past. At the end of 2008, 48 orphan drugs had obtained a Marketing Authorisation (Figure 6.4.).

Forecasting the number of Marketing Authorisations can be based on the evolution of the number of Orphan Drug Designations granted by the EC.

Figure 6.4 : Number of approved Marketing Authorisations per year and total number of Marketing Authorisations over the years 2001-2008



[Source]: DG Enterprise EC. Register of designated Orphan Medicinal Products. <<http://ec.europa.eu/enterprise/pharmaceuticals/register/orphreg.htm>>. 11/3/2009.

The figure below gives an overview of this evolution over the years since the legislation on orphan drugs exists.

Figure 6.5 : Overview of Orphan Designations 2000-2008

Year	Applications submitted	Positive COMP Opinions	Applications withdrawn	Final negative COMP Opinions	Designations granted by the Commission
2008	119	86	31	1	73
2007	125	97	19	1	98
2006	104	81	20	2	80
2005	118	88	30	0	88
2004	108	75	22	4	72
2003	87	54	41	1	55
2002	80	43	30	3	49
2001	83	64	27	1	64
2000	72	26	6	0	14
Total	896	614	226	13	593

[Source]: Committee for Orphan Medicinal Products. January 2009 Plenary Meeting, Monthly Report. EMEA. Doc. Ref.: EMEA/COMP/694107/2008. 7 January 2009. Available from <<http://www.emea.europa.eu/pdfs/human/comp/pr/69410709en.pdf>> [Last accessed: 10/3/2009].

A total of 593 designations were granted by the end of 2008.

Both the designations and the Marketing Authorisations seem to have reached a “cruise speed”, also in comparison with the situation in the USA. The estimate is therefore that there will be an average increase of at least 10 drugs per year. This figure also corresponds to expert opinions and the expectation from EMEA. There are no signs at this stage that drugs might be taken off the market. This can however be expected to happen in the longer term, for example when new therapies are introduced that replace existing orphan drugs. This has not been taken into account in the forecast as it probably will not have a significant effect in the next five years.

- Realistic scenario: net increase of 10 new orphan drugs / year
- Low growth scenario: net increase of 8 orphan drugs per year
- High growth scenario: net increase of 12 orphan drugs per year

Most of the orphan drugs that obtain a Marketing Authorisation are getting (after a delay) a positive reimbursement decision in Belgium. This has been the experience up to now, and therefore a transfer ratio of 90 % (9 out of 10 orphan drugs) has obtained a positive reimbursement decision in Belgium. This is valid for all the scenarios.

- Realistic scenario: transfer ratio of 90 %
- Low growth scenario: transfer ratio of 80 %
- High growth scenario: transfer ratio of 100 %

The average cost of a reimbursed drug over 2008 is estimated at € 2.135 million Euro. This is much higher than in 2007 when it was 1.6 million. The average of € 2.135 million is probably too low, as more than one in three orphan drugs were approved during 2008, and were introduced in the course of the year. Their budget impact will be higher in 2009. The € 2.135 million is on the other hand a high average, as it is influenced by a few drugs with a high budget impact. Many drugs are expected to have budget impacts well below that average.

- Realistic scenario: average cost of € 2.135 million / drug / year
- Low growth/cost scenario: average cost of € 2.0 million Euro / drug / year
- High growth/cost scenario: average cost of € 2.3 million Euro / drug / year

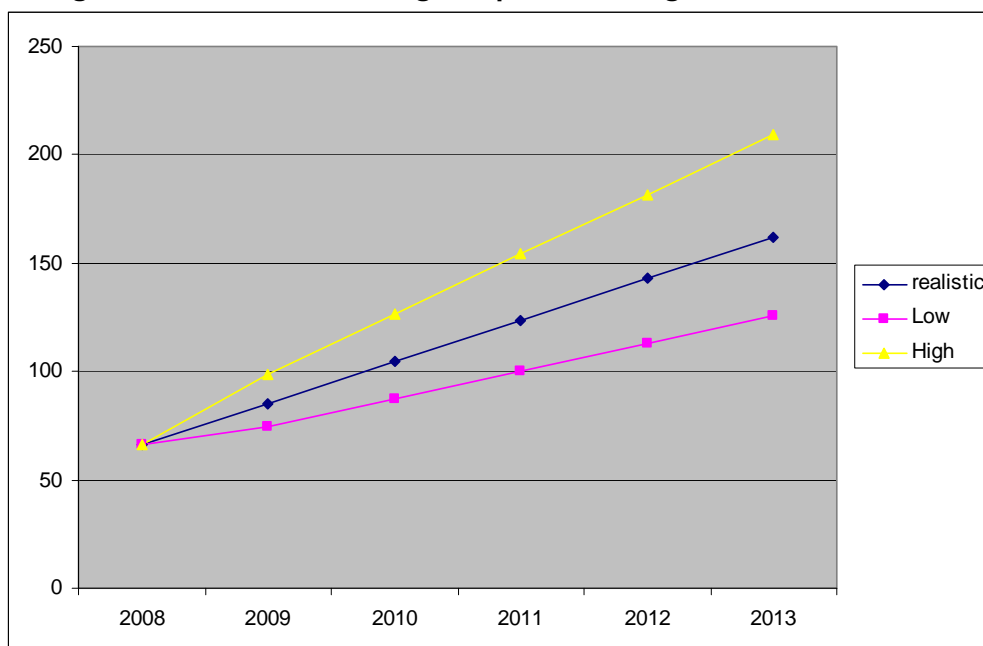
The chart below gives the results of the application of these scenarios, starting from a budget impact estimate of € 66 million for 2008. The SSF cost is not included. The application of the realistic scenario would lead to a budget impact of € 162 million in 2013 or an increase of 145 % over 5 years. Although it is (also) difficult to estimate the total cost of drugs to the budget in five years, this amount should represent close to 2 % of the total cost of drugs to the budget and over 10 % of the total drugs cost of hospitals.

This growth forecast is slower than the recent past, as based on an increase of 100 % between 2007 and 2008 (with an increase of 50 % in the number of reimbursed orphan drugs) and the estimated increase in the MORSE report¹⁰³ of the NIHD1 was 50 % between 2007 and 2008 (that estimate covered only the 18 drugs with a college).

The same restrictions that apply on the budget estimate for 2008 apply for the forecast:

- the basis for this forecast is the estimate for 2008 which combines forecasts and actual costs;
- the parameters used for the forecasts add to the uncertainty factor.

Figure 6.6 : Estimation of budget impact according to three scenario's



Key points

- For 2008, the budget impact of orphan drugs in Belgium was estimated to range from 50 to 85 million Euro, which corresponds to over 5% of total hospital drugs budgets.
- Three scenarios were applied to estimate the future budget impact: a conservative scenario (low growth/cost), a realistic scenario (best estimate) and a higher growth/cost scenario.
- It was estimated that 10 new orphan drugs would reach market each year.
- It was assumed that 90% of orphan drugs would gain reimbursement in Belgium.
- It was estimated that the average cost of a reimbursed orphan drug would amount to 2.135 million Euro per year.
- The realistic scenario would lead to a budget impact of orphan drugs of € 162 million in 2013 or an increase of 145 % over 5 years. This would represent close to 4% of the cost of all drug reimbursements to the budget and over 10 % of total drugs costs of hospitals.

7 DISCUSSION AND CONCLUSIONS

7.1 ORPHAN DRUG DESIGNATION AS A TACTICAL STEP

One of the criticisms of the present system of Orphan Designation is that it allows medicinal products for 'normal' diseases to be designated as orphan drugs.

This can happen when drugs are developed for a specific type of patients/disease (a practice called "targeting"), or when one disease is split into various sub-categories each presented with its own characteristics, a practice called "sub-setting" which is described above in the report (chapter 3):

Sub-setting can lead to so-called "salami-slicing": this is creating artificial subsets of a non-orphan condition, and basing the prevalence criterion on an unreal subpopulation. The aim is to obtain market exclusivity, a decrease of the costs and obligations linked to the registration demand, and an increase of the exclusivity through new subpopulations (also known as the "evergreening tactic").

The industry is suspected of playing it tactically by introducing drugs to the market as 'orphan', to fully reap the advantages (incentives) offered for the development of a drug with Orphan Designation, and then at a later stage to increase the number of indications for the same drug. This risk factor is increased by the fact that many oncological drugs obtain the orphan designation. As of today, one third of the orphan drugs on the Belgian market are for oncology, and their budget impact is also approximately one third of the budget impact of all orphan drugs.

The COMP is very critical about the use of these techniques and adapts its own practice accordingly. Sub-setting is allowed under conditions. However, it seems impossible to exclude completely the possibility that manufacturers turn once orphan drugs into commercially highly profitable products later on.

7.2 PREVALENCE VERSUS ECONOMIC MOTIVES

As set out in Chapter three of this report, legislation on Orphan Designation at the EU level calls on two main criteria to decide on designation: either the (low) prevalence, or the high investment needed compared to the potential income.

Both have the same underlying reasoning and are essentially considered to mean the same: a (very) low prevalence was for the legislator the equivalent to high investments for a potentially small market. The fact that both criteria are formulated as "either / or" instead of "and" has however some consequences.

Nearly all designations are granted based on prevalence. Only one designation was granted based on low 'return on investment': an Orphan Designation for a tropical neglected disease^{tt} (tuberculosis) - not a rare disease. Only five demands were filed based on the return on investment criterion. With only one approval this means a very low success rate compared to the other criterion.

Although judging the economic criteria is objectively speaking not particularly difficult, it faces a number of barriers: those who have to make the judgement have usually been trained in the field of health and do not have an economic background (hence lack the expertise) and the industry uses the argument that it is not possible to allocate costs clearly to one drug.

This situation has become an issue that requires attention for the following reasons:

- the high prices asked for orphan drugs raise the question to what extent these are indeed a fair reflection of the costs incurred by the industry – or rather just generate high profits for the industry;

tt Interview with Dr. Jordi Llinares, EMEA, on the 14th of November 2008.

- it has been demonstrated^{uu} that a few cases of orphan drugs which obviously required a very low level of investments have been brought to the market.

Some orphan drugs generate revenues of hundreds of millions Euro per year. These are not yet “blockbusters” but these drugs obviously have reimbursed their initial investments and generate a high level of return to the sponsor. The legislator has foreseen the possibility to withdraw the market exclusivity after five years. This can be done at the initiative of an EU Member State. Yet, this has never happened up to now, and it seems unlikely that any individual Member State will take this initiative. The main reason why this is unlikely to happen is the absence of an agreement on what would be an acceptable return on investment.

The overview below presents the trade-off between both interpretations of the legislation in terms of advantages and disadvantages.

	“either / or”	“and”
Advantages	Stimulates innovation because less barriers for industry	Would improve the application of the ‘spirit’ of the legislation
Disadvantages	Non-innovative, low investment drugs can obtain orphan designation	Threshold for industry would be higher

An adaptation of the legislation to “and” would potentially delay patient access to new drugs because two new barriers for the development of orphan drugs compared to the present situation would be created:

- the need for industry to provide evidence (more work);
- the need for COMP to evaluate based on economic criteria (need for additional expertise).

7.3 ASSESSING CLINICAL ADDED VALUE

Assessing the clinical added value of orphan drugs is a challenge essentially because of the low number of patients. The techniques and standards used for drugs in general to confirm clinical effectiveness are difficult to apply on orphan drugs.

At EMEA level, the clinical effectiveness is checked at the moment of deciding on Marketing Authorisation. Although the process is identical for orphan drugs compared to non-orphan drugs, there are guidelines that relate to clinical trials in small populations³².

The clinical added value is assessed first by the CHMP as part of the Marketing Authorisation process and a second time at the national level for reimbursement. The same limited information is used. The decision for market access is taken on absolute grounds (the drug is authorised to go to the market or not), the decision for reimbursement on relative grounds (‘given the alternatives, this drug is worthwhile to be reimbursed’).

At both decision levels, the analysis for orphans and for non-orphan drugs is done by the same organisations and based on the same criteria.

Considering the clinical added value, most positive decisions taken by the CHMP to grant access to the market are based on a ‘benefit of the doubt’. For orphan drugs, there is seldom proof of clinical added value at that moment.

The comparison that was performed between the work undertaken at EU level and at national level in Belgium confirms that both analyses are based on nearly identical information (see chapter 3 and 4).

^{uu} See the discussion of the ‘pricing issue’ in this chapter.

Even if the decisions to be taken on the basis of the same information are different, there are obvious efficiency gains to be achieved.

The EMEA decision process is more efficient compared to 27 individual national analyses for deciding on reimbursement. The work is actually done by two national Member States agencies, and a common opinion and decision is reached among all 27 Member States at the CHMP. Creating a similar system specifically for the assessment of clinical added value and serving as input in the national decision regarding reimbursement at EU level would seem a logical next step.

This has been suggested already at two occasions:

- Eurordis (European Organisation for Rare Diseases)¹⁰⁴ made a recommendation in this respect. This recommendation is motivated by the differences in speed of market access among Member States. Bringing this aspect to the EU level would speed up decisions in Member States and avoid the present inequalities (industry concentrating on market access in procedurally easier or larger Member States);
- The Pharmaceutical Forum¹⁰⁵ proposes an exchange of knowledge among Member States and to start an early dialogue between pricing and reimbursement authorities.

Another approach that is suggested (see chapter 2 above) is through the use of patient registries. An early patient registry, including data on the natural history of the rare disease and economically important variables, would allow regulatory authorities to follow up and evaluate long term continuous data collection and monitor the clinical efficacy over time. Setting up such patient registries is however a challenging task, as it would mean setting up a registry even before a drug is being developed. In practice it is uncertain for which rare disease a treatment will be developed. As the number of rare diseases is relatively high, questions about financing and governance of rare disease registries before the development of a treatment can be raised.

An early patient registry, including data on the natural history of the disease and economically relevant parameters, would allow regulatory authorities to follow up and evaluate the uncertainties surrounding longer-term effectiveness and cost-effectiveness of an orphan drug in the relevant population.²⁵ Such an approach would support the decision-making process and allow more timely access to orphan drugs for patients. It would however not change the actual models on which decisions are based.

The option to use disease and patient registries is described below.

7.4 THE NEED FOR A RIGHT BALANCE BETWEEN ETHICAL AND ECONOMIC CONCERNS

The development, marketing and reimbursement of orphan drugs challenge the general principles that underpin our current reimbursement policy.

The average price of orphan drugs on the market today is high, which renders the current approach to orphan drugs potentially economically unsustainable. Moreover, it may be argued that it creates inequities because the life of one person is valued higher than the life of another.²² This stretches the solidarity principle which underpins the health care system.

The quote below from the conclusions of a NHS technology assessment study on Enzyme Replacement Therapy (ERT) for Fabry disease illustrates this situation:

“Although ERT for treating the ‘average’ patient with Fabry’s disease exceeds the normal upper threshold for cost-effectiveness seen in NHS policy decisions by over sixfold, and the value for MPSI is likely to be of a similar order of magnitude, clinicians and the manufacturers argue that, as the disease is classified as an under European Union legislation, it has special status, and the NHS has no option but to provide ERT. More information is required before the generalisability of the findings can be determined. Although data from the UK have been used wherever possible, this was very thin indeed.”

Nonetheless, even large errors in assumptions made will not reduce the ICER to anywhere near the upper level of treatments usually considered cost-effective.”¹⁰⁶

The perceived extent of this problem is exacerbated by the fact that the cost-effectiveness of orphan drugs is not assessed in Belgium at the moment of the reimbursement decision - as it is considered that the information can never be sufficiently reliable due to the low number of patients.

At the same time, fair distribution principles do not allow to exclude orphan drugs altogether from being reimbursed. Reimbursement of orphan drugs fit within the objectives of health care provision and fit within our system of social solidarity in which vulnerable groups receive support.

And this may imply (limited) correction to market mechanisms. Furthermore, there is little support within the domain of social healthcare provision in general (in Belgium) for the application of a pure cost-effectiveness and efficiency reasoning.²²

The tension that currently exists between different societal concerns regarding orphan drugs needs to be addressed.

The current situation leads to individual persons following their own ‘common sense’. Those who have to take decisions in the decision-making chain, from reimbursement decision for the drug to individual patient’s eligibility, are confronted with this dilemma and potential inequity. Anecdotal evidence collected shows that this ‘tension’ can lead to decisions like patients being refused a therapy because of age although this is nowhere mentioned as a criterion.

A first step towards a solution to this situation would be to initiate a societal dialogue on the issue, to clarify what society wants and accepts in terms of ethical and economic consequences.

7.5 PRICING

From a regulatory point of view, the pricing of orphan drugs is not different to other drugs. The market conditions are however different to normal drugs.

Facts and background:

- The price is not an issue when the decision on market access is taken (EMA – Marketing Authorisation).
- The price is defined by the industry and submitted for approval to national authorities. In Belgium this is to the FPS Economy, in a process that runs in parallel to the reimbursement decision. The result is the acceptance of a maximum price. The analysis performed by the FPS Economy is mainly based on comparisons. For orphan drugs, this means comparison with other countries.
- Price negotiations are in principle not part of the drug reimbursement decision process. The price approved by the FPS Economy is considered to be the basis for reimbursement.
- There is generally no negotiation on the price. The only negotiation that may occur is by the government, between the advice of the DRC and the actual (publication of the) decision. This is mainly linked to the budget impact and can lead to a compromise with the industry to get approval. Price could be an element in the negotiation, but in practice it is not.
- The DRC could (re-)negotiate the price at regular revisions. This has however not yet happened for orphan drugs.

Small monopolies

The price is an essential element of the context created by the orphan drug legislation.

Drugs to treat rare diseases are considered as a small market, which has a number of implications:

- the investment for industry is high compared to the potential market size;
- the risks for the industry are high in terms of return on their investment.

Legitimate concerns that these factors would discourage industry from developing orphan drugs have led to legislation which aims to reduce the risks, providing incentives for investments in research for rare diseases and for the market introduction of orphan drugs. This legislation has created a comfortable situation for the pharmaceutical industry:

- they obtain market exclusivity for orphan drugs (no direct competition);
- the price is set by the industry and is not negotiated by any party.

The end result is that small 'virtual monopolies' are created in which the industry is free to ask the price they want for orphan drugs. These often high prices are justified by the need to reimburse the research and development costs.

There are however no market mechanisms in place to correct a potentially too high price:

- there is no direct or indirect competition, as is the case for other drugs;
- customers have no bargaining power towards the industry;
- the market is closed for competition: no competitor will run the risk to invest in an alternative medicinal product as the legislation blocks the (small) market access for ten years.

As such, the legislation which has a favourable impact in terms of the supply of orphan drugs to the market has, through its distortion of the market mechanisms, also the adverse effect of too high prices not being adjusted. The current rules do not, however, preclude the production of generics or biosimilars for orphan drugs once the period of market exclusivity is passed. The production of generics or biosimilars may in the medium term reduce the prices of orphan drugs.

Adding to the problem is the fact that the market for drugs in general and for orphans, is not transparent. Information on effectiveness and hence cost-effectiveness of the treatment is not available at the moment of market access, and is not available post Marketing Authorisation either. Information on clinical effectiveness is frequently (very) limited, as explained above, and decisions to grant market access are often taken allowing the 'benefit of the doubt'.

"Identical" medicines

Three of the 48 orphan drugs with Marketing Authorisation at the European level are drugs that have a "twin" product on the market. These twins are for other, non orphan indications and have a different brand name.

The orphan version of the twin is always marketed at a higher price.

The best known example is Revatio® which is another name for Viagra®. The two other products are:

- Savene® (orphan) being the same product as Cardioxane®. Savene® is sold in Belgium, Cardioxane® not. If it was available on the Belgian market, one can assume it would be prescribed instead of Savene®
- Siklos® (orphan) is identical to Hydrea®: one is delivered as capsules, the other in the form of tablets. Siklos® is not on the Belgian market and one can assume that patients of well informed medical doctors are receiving Hydrea®.

In the example of Revatio® / Viagra®, both produced by the same company, the decision to develop a different brand for the orphan indication is almost certainly not motivated by a return on investment need. Rather, the orphan drug legislation provides an additional incentive for the industry to explore and introduce the drug in a specific market niche. Since investments are largely covered by the profits generated by Viagra, the 'additional cost' is essentially linked to clinical trials and to marketing.

Compounding preparations

Two orphan drugs that obtained a market authorisation from EMEA were refused reimbursement in Belgium because of the existence of an alternative in the form of a compounding preparation.

Although both cannot be compared as one is an artisanal product and the other an industrial product, the price difference was such that it prevented approval.

Conclusion

The pricing issue is a key element of the equation. The orphan drug legislation creates a positive market environment through incentives, one of which is the creation of small virtual monopolies. Industry behaviour is to ask for high prices. Member States have little negotiation power and there are no market mechanisms in place to put a downward pressure on prices.

The spirit of the legislation, being to stimulate research and development on drugs for diseases that would otherwise be neglected by industry and academia, is put at risk by this situation, as high prices also mean high budget impacts and in general low cost-effectiveness in comparison to non-orphan drugs.

Three potential routes to solve the existing problem are:

- an adaptation of the legislation to ensure that its application happens more according to its spirit with analysis of the return on investment including subsidies received for R&D and justification of price setting;
- the application of risk-sharing systems like price-for-performance schemes or conditional reimbursements
- the organisation of price negotiations at the EU-level instead of at Member State level, which could be combined with both previous bullet points.

Advantages and disadvantages of the first two are:

	<i>Information on return on investment</i>	<i>Risk sharing</i>
advantages	<ul style="list-style-type: none"> • Is a logical consequence of the existing legislation, which should therefore be acceptable to all stakeholders 	<ul style="list-style-type: none"> • No need to provide information on investments and potential returns
disadvantages	<ul style="list-style-type: none"> • This information needs to be assessed by experts 	<ul style="list-style-type: none"> • Need to define performance criteria • Is a new technique, there is little experience with this type of price-setting (in Belgium)

7.6 EXTENSION OF INDICATIONS

Designation for an orphan drug is possible for indications with a prevalence up to 5 in 10,000.

In practice most orphan drugs are for ultra rare diseases, e.g.:

Disease	Prevalence	Orphan drug
Fabry disease	1.75 / 100,000	Fabrazyme® & Replagal®
MPS I	1.3 / 100,000	Aldurazyme®
MPS II	0.6 / 100,000	Elaprase®
MPS IV	0.4 / 100,000	Naglazyme®
Acute promyelocytic leukemia	8 / 100,000	Trisenox®
Chronic myeloid leukemia	6 / 100,000	Glivec®

Cases exist where a drug obtained the designation and Marketing Authorisation for one indication, and then later this is extended to more indications.

The legislation allows this. The same product can have more indications, and the prevalences for the various indications are not “added up”.

Orphan drugs with more than one orphan indication at European and Belgian level are:

Drug	Number of indications EMEA	Number of indications Belgium
Glivec®	6	2
Nexavar®	2	2
Sprycel®	2	1
Sutent® ^{vv}	2	2
Tracleer®	2	2

Changing the legislation to link the designation as orphan drug to the total prevalence of all indications would have consequences as described in the table below:

	Advantage	Disadvantage
Change the legislation	<ul style="list-style-type: none"> • Would be more in line with spirit of legislation • Would ensure to concentrate on really rare • Would create a barrier to use the OD legislation for purposes it was not meant for 	<ul style="list-style-type: none"> • Creates a potential barrier to develop new product-indication combinations

^{vv} Sutent® has withdrawn its orphan designation at EMEA level

7.7 GROWTH OF THE BUDGET IMPACT OF ORPHAN DRUGS

Total budgets for orphan drugs were very small when the legislation was launched in 2000.

Today they have become significant, even if the total number of patients treated is still limited.

This high growth is powered by a number of factors:

- the high average price of orphan drugs;
- the steady increase in the number of orphan drugs coming to the market.

In Belgium, there is no budget ceiling for orphan drugs, but the total cost of all drugs reimbursed does have a ceiling. When the global ceiling is reached, there are mechanisms to compensate for over-expenditure. The government can charge an alternative charge to the pharmaceutical industry to compensate 100% of the over-expenditure, with a maximum of €100 million per year. Orphan drugs do not contribute to this subsidiary charge. Orphan drugs as a group have no ceiling.

The budget increase of orphan drugs therefore puts pressure on the total ceiling, and non orphan drugs industry is likely to pay for the orphan drugs industry.

The cost of orphan drugs in Belgium is estimated to have been over 5 % of total hospital drug budgets in 2008^{ww} and further estimates indicate the future cost could be well above 10 % of hospital drug budgets in five years from now. Orphan drugs represent probably 2% of total drug reimbursement costs in 2009, and could represent close to 4% in 2013.

This high cost creates an upward pressure on health insurance budgets. If and when hundreds of orphan drugs become available, they would still cover only part of the needs of all the patients suffering from rare diseases. Moreover, relatively large amounts of the limited health care budget would go to a few patients, which may challenge the boundaries of solidarity. Based on the experience with a first set of 31 orphan drugs, the cost to the health insurance system under the present conditions could become unbearable.

The high prices combined with the growing budget impact of orphan drugs also negatively affect the image of the orphan drugs among decision-makers. Globally speaking, the orphan drug legislation is considered by all parties to be a success. The price of this success is the rising budget. The negative image created puts the success at risk.

7.8 VARIATIONS IN ACCESS AND USE AMONG MEMBER STATES

Although the Marketing Authorisation decision grants access to the market in 27 Member States, because of the cost of the drugs, effective access is reached only when the decision is taken to reimburse the medicinal product (at the national level).

As a consequence, the effective market access and the utilization of orphan drugs vary among Member States.

The situation of Belgium compared to other countries analysed can be summarised as follows:

- Starting a process to decide on reimbursement of a drug is the initiative of industry. In practice, Belgium is not one of the countries that is chosen as a priority by industry.

ww The number of individual patients treated is difficult to estimate both for orphan drug treatments and for hospital treatments, but one speaks of a difference in cost/treatment/patient that must be in the around one (for non orphan drugs) to one thousand (for orphan drugs).

- Out of the 47 orphan drugs having obtained Marketing Authorisation by end 2008, 31 are reimbursed in Belgium and 4 are not reimbursed. This puts Belgium at third place compared to France, Italy, the Netherlands and Sweden (see point 4.9).^{xx}
- The procedure to access reimbursement in Belgium takes in theory 180 days, but will in practice, due to interruptions, last longer. There is little evidence that this process ends up to be much longer than in other Member States, but industry mentions this as the argument to be reticent to start reimbursement procedure. In comparison, an orphan drug having obtained Marketing Authorisation is automatically launched on the British market. But if the advice of NICE is requested for reimbursement, the procedure can be slow (see point 4.8).
- In Belgium three systems exist for early access: the SSF, the medical needs programme and the compassionate use legislation (see 4.3.3.2 and 4.3.3.3). The SSF de facto plays a role between Marketing Authorisation and reimbursement decision. It can be questioned if the SSF is an adequate mechanism for that purpose (awareness of patients and Medical Doctors, criteria, etc.).

Early access (before Marketing Authorisation)

In Belgium, early access is possible through the Special Solidarity Fund (see point 4.3.3.3).

Figure 7.1 : SSF reimbursement for Orphan Drugs with MA in 2007

Orphan drug	Total NIHDI Expenditures	Number of patients	NIHDI expenditures per patient
Myozyme®	€ 3,540,723	7	€ 505,818
Revatio®	€ 299,358 €	67	€ 4,468
Revlimid®	€ 141,050 €	57	€ 2,475
Ventavis/Iloprost®	€ 100,927 €	9	€ 11.214
Tracleer®	€ 2,167 €	1	€ 2,167

Source: NIHDI. Jaarverslag 2007 betreffende het Bijzonder Solidariteitsfonds, 2008

Several Member States have a particular procedure providing early access:

- In France, orphan drugs can be accessed before they are reimbursed, through the 'Authorisation for Temporary Use' (ATU) procedure (see point 4.4).
- A special fund for compassionate use was set up in Italy in order to finance early access to orphan drugs and trials on rare diseases (see point 4.5).

xx Information about the United Kingdom is not available.

7.9 AWARENESS RAISING

Because of the low incidence of rare diseases, health professionals generally have a low awareness and little knowledge on how to treat such diseases.

This explains the importance and focus of the EU level actions and national plans for rare diseases on:

- developing awareness raising actions and tools;
- developing tools to give access to knowledge and expertise including data-bases;
- building expertise in specialized centres; for many Member States this implies to refer patients with a specific disease to a specific expert centre;
- the added value of EU and international cooperation.

The concept of “orphan drug” is a non-reality for the medical professionals. Their concern is the patient, the disease and the potential treatment. Whether the drug is an orphan drug or not has no importance. “Orphan drugs” is a technical concept, not understood, not commonly used by health professionals.

Even for specialists on rare diseases and orphan drugs, there exists confusion on which drugs are “orphan” and which are not. Indeed, there exists a ‘grey zone’:

- drugs for orphan indications that do not have the orphan status, either because they were introduced before the legislation, or because they are also used for non-orphan indications; some of these drugs do have the orphan status in the USA but (not yet) at EU level;
- there is one drug that has the orphan status in Belgium but not at EU level^{yy};
- there are various drugs with orphan status at EU level or in the US, that are not reimbursed in Belgium;
- etc.

The only efficient solution to close this awareness gap seems to be to concentrate expertise. The route of setting up expert centres for rare diseases will also be beneficial for the promotion of therapies using the right orphan drug.

7.10 COLLEGES AND CONTROL OF ELIGIBILITY

In Belgium, orphan drugs can only be prescribed to individual patients if a number of conditions are met. These are defined by the DRC at the moment of the decision to put the drug on the list of reimbursed orphan drugs. Medical Doctors who wish to prescribe the drug have to ensure these conditions are met and confirm this when sending the application for the reimbursement to the health insurance organisations.

In principle, this is linked to the control of the eligibility. It also serves to collect information that could be used later for revisions of decisions.

In practice, the perception by Medical Doctors and the industry is that criteria and conditions (of which the relevance is not always clear) are added as a technique to create barriers to the use of orphan drugs. Examples are the need to renew the demand every six or twelve months for life-time diseases, or to repeat tests at regular intervals, which leads to (unnecessary) costs and a sometimes heavy physical and mental burden for the patient. This perception seems to be exacerbated by a lack of transparency and of return on the information provided.

^{yy} Duodopa®, which obtained the designation at national level in 2006; this would not be possible anymore today.

The Colleges of Orphan Drugs, when they exist, have the power to adapt and change these conditions, based on experience. This is apparently working, but is not done systematically or pro-actively although the Colleges do have a formal responsibility in this respect. It does put an additional burden and responsibility on the Colleges.

The following observations can be made in relation to the functioning and the role of the Colleges:

- the establishment of Colleges seems to be a good technique, as it allows to bring together the (rare) expertise;
- the sickness funds are not legally required to ask the advice of the Colleges, but they nevertheless have a consensus to request it systematically;
- the work volumes for these Colleges is very high, and the increase in the number of orphan drugs leads to the need to create a permanent support structure;
- Colleges are reactive in their functioning; they do have a permanent structure but with little resources. With more resources, they could become more pro-active and propose changes and improvements;
- their success raises the question as to what to do with the thirteen drugs out of 31 that have no College: should this not be systematic? ;
- if a sickness fund takes a negative decision, it has the theoretical obligation to inform the College but there is little evidence that this leads to additional knowledge. If the Colleges reviewed all requests and registered systematically all decisions, both positive and negative, they would be in a better position to provide advice and information at the moment of revisions;
- Colleges potentially pool a lot of information; it would be easy to ensure they concentrate all information. For the moment, the collected information is not easily available, e.g. the year reports are not publicly available. Making the information publicly available would improve the efficiency, also to decide on revisions.

Typology of the Colleges:

Total number of Colleges	18
Therapeutic area	Endocrinology/Metabolism: 10 Neurology: 1 Cardiovascular/respiratory: 3 Oncology: 3 Haematology: 1
First or second line	11 First 1 First/second 6 Second
Alternative?	9 have an alternative versus 9
Treatment	8 peroral (by mouth) 10 paranteral

7.11 USE OF REGISTRIES

Patient or disease registries^{zz} are used for various purposes and particularly in the case of rare diseases. Setting up patient and disease registries is part of the EU policy and is an action line in national rare disease plans that many Member States have or are setting up.

Typical purposes why registries are being set up are:

- to describe the natural history of a disease;
- for research purposes (e.g. to have fast access to patients);
- to determine clinical effectiveness;
- to monitor cost-effectiveness;
- to monitor safety and harm.

Registries are set up for rare diseases before and independently of the fact a medicinal product is being developed. As there are an estimated 5,000 to 8,000 rare diseases, it is clear that registries exist for only part of the rare diseases.

With regard to orphan drugs, there are two moments when registries are usually set up:

- at the moment of Marketing Authorisation. The CHMP will on an ad hoc basis impose on the industry to set up a registry. This can be for various purposes mainly linked to the clinical effectiveness and/or the safety and harm monitoring;
- at the moment of the decision on reimbursement, national authorities can also decide that setting up a registry is a condition for reimbursement.

Each of these decisions is ad hoc, there is no standardisation, neither at EMEA level, nor at the level of individual Member States, nor among Member States.

An exception is the MPS registry in the UK, that was set up before a drug for MPS was developed.

The industry is in charge of funding and setting up these registries which goes against the important principle that data should be “independent” in the case of registries. They do this adequately but can decide autonomously on how and according to which standards it will be set up and managed nearly always by third parties.

The existence of registries for the indications of orphan drugs is generally considered as an advantage offsetting the potential disadvantages (e.g. cost or privacy issues) and the difficulties linked to their management particularly to ensure their long term sustainability beyond the point in time where obligations for the EMEA are fulfilled. The main advantages are:

- access to patients: both for research and market access (linked to the rarity);
- transparency: it is a source of information for those who need to decide on the most adequate therapy (effective treatment);
- control: it is a way for the reimbursement authorities to control whether the medicine is prescribed for the right type of patients, as well as to gain insights on whether the therapy is working and should be continued.

^{zz} **Disease registry** is a specially designed database with voluntary, observational clinical data collected from physicians and intended to explore and define the natural course and clinical characteristics of disease, as well as to track and characterize response to treatment.

Patient register is a database (list) containing baseline information on the existence of patients with (a) certain disease(s), but without any longitudinal follow-up. (Working Group Pricing and Reimbursement. Improving access to orphan medicines for all affected EU citizens. The Pharmaceutical Forum. 2008. Available from <http://ec.europa.eu/pharmaforum/docs/pricing_orphans_en.pdf> [Last accessed: 10/12/2008].)

Willingness to participate in patient and disease registries is high among the medical professionals, which contrasts with their reluctance to provide a lot of information linked to the decisions for individual reimbursement. This difference is explained by the return for the Medical Doctor, which is real with a registry and most often absent for the latter.

Transparency is an important value in the case of orphan drugs. Decisions on market authorisation are based on limited clinical evidence. Reimbursement decisions are based on the same limited clinical evidence, but are furthermore taken without information on cost-effectiveness. When the medicinal product is on the market, the normal market mechanisms are not working as there is no alternative to the treatment which is reinforced by the orphan drug legislation (market exclusivity). The transparency achieved through registries can compensate for this, especially by providing growing evidence on both the clinical effectiveness and the cost-effectiveness of the treatment.^{aaa}

Various routes exist to improve the use of registries in the case of orphan drugs:

1. systematically setting up patient registries for all indications for which designations were granted; this will create value for all those involved later in the decision-making, including industry who will have easier access to patients, and for reimbursement authorities who can forecast the budget impact more precisely;
2. standardizing the registries, at the EU level for clinical evidence;
3. ensure coordination for aspects of clinical evidence between what is asked at EU level and what is asked at national level;
4. systematically set up data collection on cost-effectiveness of treatments through registries;
5. coordinate the cost-effectiveness information to be collected between Member States.

This subject is worth a study on its own, but it is clear that value can be created through:

- standardization and coordination between the various decision-makers;
- collecting information on the effectiveness of the treatments / drugs after their introduction on the market. This will improve the quality of information available when revising reimbursement decisions;
- transparency: it will allow the “market” to function better by ensuring the information flows.

^{aaa} An analysis based on the registry has however no added value for the assessment of the “incremental” cost-effectiveness of that respective drug, as such assessment requires a comparison with the “best alternative treatment”. Cost benefit can only be compared if data on the alternative treatment is available. A registry is (only) a way to monitor the effectiveness of a medicinal product.

Key points

- **The present system of Orphan Designation allows for medicinal products for 'normal' diseases to be designated as orphan drugs.**
- **The economic factors underlying Orphan Designation can be questioned in some cases as a low prevalence does not equal potential low return on investment.**
- **Evidence about clinical added value of orphan drugs is rarely available at the moment of registration due to the low number of patients. European cooperation can lead to significant efficiency gains, particularly through the use of patient registries.**
- **There is a need to find a right balance between ethical and economic concerns as this leads to tensions. A solution could be to initiate a societal dialogue on the issue, to clarify what society wants and accepts in terms of ethical and economic consequences**
- **In essence, small monopolies are created to stimulate development and supply of orphan drugs, but there are no market mechanisms to adjust prices once drugs are on the market.**
- **The growing impact of orphan drugs on the total budget for health insurance in Belgium is creating pressures.**
- **Indications can be extended for an orphan drug and the total prevalence across indications is not considered.**
- **Access of Belgian patients to orphan drugs in practice depends on the manufacturer submitting a reimbursement application and on the Drug Reimbursement Committee granting reimbursement.**
- **Health professionals generally have a low awareness of rare diseases and orphan drugs due to their rare occurrence.**
- **There is a need for a comprehensive approach towards defining and exercising the role of the Colleges of Orphan Drugs.**
- **There is a need for a European standardised approach to setting up and using patient and disease registries. Centralisation will also increase the chances of long term sustainability.**

8 APPENDICES

8.1 OVERVIEW REIMBURSED ORPHAN DRUGS IN BELGIUM

Drug	Indication	Sponsor	EMEA		NIHDI		
			Orphan Designation	MA	Submission date	Approval date	Reimbursed since
Aldurazyme®	Treatment of Mucopolysaccharidosis, type I	Genzyme	14/2/2001	10/6/2003	26/6/2003	20/7/2004	1/8/2004
Atriance®	Acute lymphoblastic leukaemia	GSK	16/6/2005	22/8/2007	19/9/2007	21/5/2008	1/6/2008
Busilvex®	Hematopoietic cell transplantation	Pierre Fabre Medicament	29/12/2000	9/7/2003	7/6/2004	13/12/2004	1/10/2008
Carbaglu®	NAGS deficiency	Orphan Europe	18/10/2000	24/1/2003	7/12/2005	21/8/2006	1/9/2006
Duodopa®	Parkinson	Solvay	/	/	7/7/2006	16/2/2007	1/3/2007
Elaprase®	Mucopolysaccharidosis, type II (Hunter Syndrome)	Shire	11/12/2001	8/1/2007	13/3/2007	20/12/2007	1/1/2008
Evoltra®	Acute lymphoblastic leukaemia	Genzyme	5/2/2002	29/5/2006	7/1/2008	20/6/2008	1/7/2008
Exjade®	Chronic iron overload requiring chelation therapy	Novartis Pharma	13/3/2002	28/8/2006	6/11/2006	20/6/2007	1/8/2007
Fabrazyme®	Fabry disease	Genzyme	8/8/2000	4/5/2001	8/4/2002	20/7/2004	1/8/2004
Glivec®	Chronic myeloid leukaemia	Novartis	14/2/2001	27/8/2001	7/7/2003	19/3/2004	1/7/2003
	Malignant gastrointestinal stromal tumours				5/8/2002	20/6/2003	
Increlex®	Treatment of primary insulin-like growth factor-I deficiency due to molecular or genetic defects (primary growth hormone insensitivity syndrome)	Ipsen	22/5/2006	3/8/2007	3/12/2007	18/7/2008	1/8/2008
Lysodren®	Adrenal cortical carcinoma	HRA Pharma	12/6/2002	28/4/2004	21/11/2006	20/12/2007	1/1/2008
Myozyme®	Glycogen Storage Disease type II (Pompe's disease)	Genzyme	14/2/2001	29/3/2006	18/5/2006	20/4/2007	1/5/2007
Naglazyme®	Treatment of Mucopolysaccharidosis, type VI (Maroteaux-Lamy Syndrome)	Biomarin Europe	14/2/2001	24/1/2006	21/11/2007	20/11/2008	1/12/2008

Drug	Indication	Sponsor	EMA		NIHDI		
			Orphan Designation	MA	Submission date	Approval date	Reimbursed since
Nexavar®	Renal cell carcinoma	Bayer Healthcare	29/7/2004	19/7/2006	1/8/2006	21/3/2007	1/4/2007
	Hepatocellular carcinoma				2/10/2007	20/6/2008	1/7/2008
Orfadin®	Tyrosinaemia type I	Swedish Orphan	29/12/2000	21/2/2005	3/8/2005	20/6/2006	1/7/2006
Replagal®	Fabry disease	TKT-Europe / Shire	8/8/2000	4/5/2004	Unknown	Unknown	1/8/2004
Revatio®	Pulmonary Arterial Hypertension	Pfizer	12/12/2003	28/10/2005	24/5/2006	21/5/2007	1/6/2007
Revlimid®	Multiple Myelome	Celgene	12/12/2003	14/6/2007	19/7/2007	21/3/2008	1/4/2008
Savene®	Anthracycline extravasations	Topotarget	10/9/2001	28/7/2006	14/12/2006	21/8/2007	1/9/2007
Somavert®	Acromegaly	Pfizer	14/2/2001	13/11/2002	27/6/2003	19/3/2004	1/4/2004
Sprycel®	Chronic myeloid leukaemia	Bristol-Myers Squibb	23/12/2005	20/11/2006	14/12/2006	21/8/2007	1/9/2007
Sutent®	Malignant gastrointestinal stromal tumours	Pfizer			9/8/2006	21/3/2007	1/4/2007
	Renal cell carcinoma				8/2/2007	20/7/2007	1/8/2007
Tasigna®	Chronic myeloid leukaemia	Novartis Pharma	13/4/2007	19/11/2007	17/12/2007	21/8/2008	1/9/2008
Thalidomide®	Multiple Myelome	Celgene	20/11/2001	16/4/2008	Unknown	Unknown	18/09/1999
Thelin®	Pulmonary Arterial Hypertension	Pfizer / Encysive UK Ltd	21/10/2004	10/8/2006	19/4/2007	20/12/2007	1/1/2008
Torisel®	Renal cell carcinoma	Wyeth	6/4/2006	19/11/2007	4/1/2008	20/11/2008	1/12/2008
Tracleer®	Pulmonary Arterial Hypertension	Actelion	14/2/2001	15/5/2002	8/1/2003	20/7/2004	1/8/2004
	Chronic thromboembolic pulmonary hypertension				21/12/2005	21/8/2006	1/9/2006
Trisenox®	Acute promyelocytic leukaemia	Cephalon	18/10/2000	5/3/2002	16/2/2005	20/10/2005	1/11/2005
Xagrid®	Essential thrombocytose	Shire	29/12/2000	16/11/2004	24/1/2005	20/10/2005	1/11/2005
Zavesca®	Gaucher disease	Actelion	18/10/2000	20/11/2002	30/11/2004	19/8/2005	1/9/2005

8.2 CHARACTERISTICS OF ORPHAN DRUGS SUBMITTED FOR REIMBURSEMENT IN BELGIUM, 2004-2008

Orphan drug (ATC code)	Reimbursement application		Therapeutic value		Therapeutic needs		Budget impact		Supplier	Number of indications (EMA // Belgium)
	Original or revision	Reimbursed	Number / design	Evidence published	First or second line	Alternative	Number of patients	Cost per patient per year		
Aldurazyme® (A16AB05)	Revision	Yes	1 RCT	No	First	No	12	€ 40,000	Genzyme	1 // 1
Atriance® (L01BB07)	Original	Yes	2 case series	Yes	Second	No	5 children, 19 adults	€ 23,000 (adult), € 14,000 (child)	GSK	1 // 1
Busilvex® (L01AB01)	Original	No	2 open-label studies	Yes	Second	Yes			Pierre Fabre Médicament	1 // 0
Carbaglu® (A16AA05)	Original	Yes	2 case series	No	First	No	5-6	€ 14,000- 1,100,000	Orphan Europe	1 // 1
Duodopa® (N04BA02)	Original	Yes	2 case series	No	First	Yes	80	€ 41,000	Solvay Pharma	0 // 1
Elaprase® (A16AB09)	Original	Yes	1 RCT	Yes	First	No	13	€ 300,000	Shire	1 // 1
Exjade® (V03AC03)	Original	Yes	1 RCT, 1 case series	Yes	First / second	Yes	450-1,150	€ 12,000-23,000	Novartis pharma	1 // 1
Fabrazyme® (A16AB04)	Revision	Yes	2 RCTs, 3 case series	Yes	First	Yes	50-75	€ 195,000€	Genzyme	1 // 1
Glivec® (L01XE01)	Original	No			First / second	No		€ 48,000	Novartis	6 // 2
Lysodren® (L01XX23)	Original	Yes	Case series	No	First	No	36	€ 167,000	Laboratoire HRA Pharma	1 // 1
Myozyme® (A16AB07)	Original	Yes	2 open-label studies, 2 case series	No	First	No	24 children, 51 adults	€ 55,000- 328,000€	Genzyme	1 // 1
Nexavar® (L01XE05)	Original	Yes	1 RCT	Yes	Second	Yes	120	€ 50,000	Bayer Healthcare	2 // 1
Orfadin®	Original	Yes	Case series	No	First	Yes	11	€ 100,000	Swedish Orphan	1 // 1

Orphan drug (ATC code)	Reimbursement application		Therapeutic value		Therapeutic needs		Budget impact		Supplier	Number of indications (EMEA // Belgium)
(A16AX04)									International	
Replagal® (A16AB03)	Revision	Yes	3 case series	No	First	Yes	50-75	€ 200,000	Shire EGT	1 // 1
Revatio® (G04BE03)	Original	Yes	2 RCTs	Yes	First / second	Yes	105	€ 7,000-26,000	Pfizer	2 // 1
Revlimid® (L04AX04)	Original	Yes	2 RCTs	No	Second	Yes	200	€ 60,000	Celgene	1 // 1
Savene® (V03AF02)	Original	Yes	2 case series	No	First	No	29	€ 10,000	Topotarget	1 // 1
Somavert® (H01AX01)	Original	Yes	1 case series	Yes	Second	No	70	€ 47,000	Pfizer	1 // 1
Sprycel® (L01XE06)	Original	Yes	6 case series	Yes	Second	Yes	85	€ 56,000	Bristol-Myers	2 // 1
Sutent® (L01XE04)	Original	Yes	1 RCT	No	Second	Yes	73	€ 16,000	Pfizer	2 // 2
	Original	Yes	2 case series	Yes	Second	Yes	180-240	€ 20,000		
Thelin® (C02KX03)	Original	Yes	3 RCTs	No	First / second	Yes	300	€ 32,000	Encysive	2 // 2
Tracleer® (C02KX01)	Original	Yes	2 RCTs	No	First	Yes	300	€ 40,000	Actelion Registration Ltd	2 // 2
Trisenox® (L01XX27)	Original	Yes	2 case series	Yes	Second	No	9	€37,000	Cephalon	1 // 1
Wilzin® (A16AX05)	Original	No				Yes			Orphan Europe	1 // 0
Xagrid® (L01XX35)	Original	Yes	6 case series	Yes	Second	No	1,100	€8,000	Shire Pharmaceutical	1 // 1
Zavesca® (A16AV06)	Original	Yes	1 open-label study, 2 case series	Yes	Second	Yes	90	€ 93,000	Actelion	1 // 1

8.3

QUALITATIVE QUESTIONNAIRE BENCHMARKING**THE RARE DISEASE AND ORPHAN DRUG MARKET:****Questionnaire**

Instructions: Please respond to questions electronically. You can move forward through the main body of the questionnaire by pressing "Tab" and backwards by pressing "Shift + Tab", or you can use the scroll feature and the mouse. Boxes can be ticked and ticks can be removed by double-clicking the mouse.

Identification

Country Name:	
---------------	--

Contact Details for the Person Completing the Form

Name:	
Title:	
Institution:	
Address:	
Country:	
Telephone:	
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Section I. Institutional context of orphan diseases/orphan drugs	
I.1.	Identify and list centres for orphan diseases:
I.2.	Identify and list policy measures that promote specifically the development of orphan drugs:
I.3.	Identify and list specific programmes to fund research networks on orphan diseases and on orphan drugs:
I.4.	Identify and list incentives for research on orphan diseases and on orphan drugs:
I.5.	Any additional comments on the institutional context surrounding orphan diseases and orphan drugs:
I.6.	Are thresholds defined for reimbursement decisions for drugs expressed in QALY or similar? Yes: <input type="checkbox"/> No: <input type="checkbox"/>
.a	If "Yes", what is the threshold:

.b	Is this threshold also applied for orphan drugs? Or a different threshold?	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
.c	If a different threshold is used, which one:	
.d	Do you expect changes in this regard in the short to medium term?	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
.e	If yes, please explain:	
1.7.	Is there a national definition for “orphan disease” and/or “ultra-rare disease”?	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
.a	If “Yes”, give the definition and its source:	

Section 2. Marketing Authorisation of orphan drugs		
2.1.	Is there a national procedure for granting Marketing Authorisation of orphan drugs instead of the EMEA procedure? <i>If "No", go to question 2.2.</i>	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
.a	If “Yes”, name the organisation in charge of the national procedure for Marketing Authorisation:	
.b	If “Yes”, specify how long it takes to obtain a Marketing Authorisation (i.e. the duration of the application procedure):	
.c	If “Yes”, specify the various criteria that are used to judge an application:	
2.2.	Is there a procedure for compassionate use of orphan drugs? <i>If "No", go to question 2.3.</i>	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
.a	If “Yes”, specify the various criteria for compassionate use of orphan drugs:	
2.3.	Is there a procedure for off-label use of orphan drugs? <i>If "No", go to question 2.4.</i>	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
.a	If “Yes”, specify the various criteria for off-label use of orphan drugs:	
2.4.	Any additional comments on Marketing Authorisation of orphan drugs:	

Section 3. Pricing of orphan drugs	
3.1.	Describe the mechanism by which prices of orphan drugs are set:
.a	Free market pricing: Yes: <input type="checkbox"/> No: <input type="checkbox"/>
	If "Yes", describe system of free market pricing:
.b	Fixed pricing: Yes: <input type="checkbox"/> No: <input type="checkbox"/>
	If "Yes", describe system of price fixing:
.c	Other (please specify): Yes: <input type="checkbox"/> No: <input type="checkbox"/>
3.2.	Describe the principal bodies or agencies that are involved in pricing of orphan drugs:
3.3.	Is there a procedure for revising prices of orphan drugs on national/regional lists? If "No", go to question 3.4. Yes: <input type="checkbox"/> No: <input type="checkbox"/>
.a	If "Yes", describe which factors are taken into account when revising prices (e.g. change in production costs, evolution of price index):
.b	If "Yes", indicate how often prices are revised:
3.4.	Any additional comments on pricing system of orphan drugs:

Section 4. Reimbursement of orphan drugs	
4.1.	Describe the mechanism by which reimbursement of orphan drugs is set:
.a	Public procurement at national level: Yes: <input type="checkbox"/> No: <input type="checkbox"/>
	If "Yes", describe system of tendering:
.b	Public procurement at regional/local level: Yes: <input type="checkbox"/> No: <input type="checkbox"/>
	If "Yes", describe system of tendering:
.c	National list of tariffs: Yes: <input type="checkbox"/> No: <input type="checkbox"/>
	If "Yes", specify how tariffs are set:
	Also, specify name of national list:
.d	Regional list of tariffs: Yes: <input type="checkbox"/> No: <input type="checkbox"/>
	If "Yes", specify how tariffs are set:
	Also, specify name of regional list:
.e	Other (please specify): Yes: <input type="checkbox"/> No: <input type="checkbox"/>
4.2.	Which third-party payer reimburses orphan drugs? National Health Service <input type="checkbox"/>
.a	(tick appropriate box) Social insurance: Public <input type="checkbox"/> Private <input type="checkbox"/> Combination <input type="checkbox"/>
.b	Describe the process and decision criteria that are used for admitting a new orphan drug to the system of third-party payer reimbursement:
.c	Describe the process and decision criteria that are used for determining the level of third-party payer reimbursement of a new orphan drug:
.d	Are there any restrictions/conditions for reimbursement of orphan Yes: <input type="checkbox"/> No: <input type="checkbox"/>

	drugs?	
.e	If "Yes", describe restrictions/conditions:	
	Specify the level of patient co-payments for orphan drugs:	
4.3.	Any additional comments on reimbursement system of orphan drugs:	
4.4.	Is the reimbursement decision based on the EMEA dossier and/or the ICH report? If "Yes", please describe how these documents are used:	

Section 5. Distribution channels

5.1.	Describe principal bodies or agencies that dispense orphan drugs to patients:	
.a	Hospital pharmacies:	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
.b	Community pharmacies:	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
.c	Health authorities:	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
.d	Internet:	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
.e	Other (please specify):	Yes: <input type="checkbox"/> No: <input type="checkbox"/>

Section 6. Prescribing process

6.1.	Describe the mechanism by which orphan drugs are prescribed:	
.a	Which party issues the first prescription? (<i>tick one or more appropriate boxes</i>)	Specialist physician <input type="checkbox"/> Nurse practitioner <input type="checkbox"/> General practitioner <input type="checkbox"/>
.b	Are there any conditions for prescribing orphan drugs? <i>If "No", go to question 6.2.</i>	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
	If "Yes", describe conditions:	
6.2.	Is there any control mechanism?	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
	If "Yes", please describe this control mechanism:	
6.3.	Are there differences in individual reimbursement decisions depending on:	
	Region	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
	Orphan drug	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
	Other:	Yes: <input type="checkbox"/> No: <input type="checkbox"/>
	Please describe these differences:	
6.4.	Any additional comments on prescribing process of orphan drugs:	

Thank you for your assistance
Please return questionnaire by e-mail to:
Christel.Fostier@yellowwindow.com

8.4 QUALITATIVE QUESTIONNAIRE PHARMACEUTICAL INDUSTRIES

Questionnaire Study “Orphan Diseases and Orphan Drugs”

Contact details for the person completing the form

Name:	
Title:	
Institution:	
Address:	
Country:	
Telephone:	
Fax:	
Email:	

Correspondence address:

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1. Pros and cons of the system of orphan drug based on experience with this specific drug

- a. Pros:
- b. Cons:

2. Orphan Designation

- a. The designation is acquired if the medical product fulfils one of the following criteria: either / or prevalence versus economic motives. Which criterion was used in this case?
 - prevalence
 - economic
- b. Has anything changed since the designation in this respect (either prevalence or economic)

3. FDA versus EMEA

- a. Is the situation for this drug different in the USA and EU or is it likewise?
 - different
 - same
- b. If different, what are those differences?

4. Post-Marketing Authorisation

- a. Have you obtained MA under exceptional circumstances or a conditional MA?
 - exceptional
 - conditional
 - none
 - i. If exceptional or conditional, under what conditions:
 - ii. What is the actual status? (Still exceptional/conditional?)

- b. Have you set up a patient register? yes
 no
- i. Is this imposed or is it a free decision? yes
 no
- ii. Who is managing the register?

5. Post-reimbursement

- a. Forecast of number of patients done at start versus actual number of patients identified: versus
- b. Forecast budget impact versus actual budget impact: versus
- c. How did you experience the interaction with the College of Orphan Drugs?
- d. Do all patients have access or do you notice that patients face barriers to get access? all have access
 barriers
- i. What types of barriers are faced?
- ii. If applicable: how many / what is the proportion of patients that do not have access?
- e. Do you consider that conditions imposed to obtain reimbursement are adequate? yes
 no
- i. If not, in what sense? Has or is this changing overtime?
- ii. Who plays a leading role in changing/adapting those conditions/rules?

6. Present situation: could you fill in the table below for following questions

- a. How many patients are there in each country?
- b. What is the price of the drug in following countries?
- c. What is the turnover in each country?

	Belgium	France	Nether-lands	UK	Italy	Sweden
Number of patients						
Price						
Turnover						
Date of market introduction						

- d. Do you consider all patients to have been identified or do you expect the number of patients to grow? (in Belgium)

Thank you for your assistance
 Please return questionnaire by e-mail to:
christel@yellowwindow.com

8.5 LIST OF EXPERTS AND STAKEHOLDERS CONSULTED FOR THE STUDY

8.5.1 List of interview respondents

Respondent	Institution	Date
Dr Ségolène Aymé	Orphanet	4/7/2008
Mr André Lhoir	Federal Agency for Medicines and Health Product (Belgium)	12/9/2008
Mr Marc Doods	UZ Leuven (Belgium)	30/9/2008
Dr David Cassiman	UZ Leuven (Belgium)	30/9/2008
Mr Daniel Brasseur	EMA	1/10/2008
Mr Erik Tambuyzer	Genzyme	7/10/2008
Mr Erik Brouwer Ms Katrien Van Geyt Ms Annemie Mertens	Genzyme	20/10/2008
Dr Jordi LLinares	EMA	14/11/2008
Mr Alastair Kent	Genetic Interest Group (United Kingdom)	20/11/2008
Ms Françoise Marlier	FPS Economy (Belgium)	12/2/2009
Mr François Arickx	NIHDI (Belgium)	13/2/2009
Ms Minne Casteels	NIHDI (Belgium)	16/2/2009
Mr Michael Berntgen	EMA	18/2/009
Mr Philippe Van Wilder	NIHDI (Belgium)	2/4/2009
Mr Paul De Keyser	Independent consultant for pharmaceutical industries	7/4/2009

8.5.2 Consultations

Consultation and exchanges took place with the Fund Rare Diseases and Orphan Drugs of King Baudouin Foundation (Belgium), including participation in their meetings on the 19th of September and 14th of October 2008.

A consultation took place with Pharma.be on the 7th of April 2009: presentation of the study and consultation on the main issues.

8.5.3 National experts

- France: Mrs Annie Lorence of the Afssaps
- Italy: Dr Pierre Folino Gallo of the Italian Medicines Agency
- Netherlands: Dr Sonja Van Weely of the Dutch Steering Committee Orphan Drugs
- Sweden: Mr Karl Arnberg of the Dental and Pharmaceutical Benefits Board
- United Kingdom: Ms Martina Garau of the Office of Health Economics

8.6 LIST OF 14 ORPHAN DRUGS USED FOR EMEA – NIHDI COMPARISON

1. Aldurazyme ®
2. Atriance ®
3. Elaprase ®
4. Fabrazyme ®
5. Nexavar ® (for indications RCC and HCC)
6. Replagal ®
7. Revatio ®
8. Revlimid ®
9. Sprycel ®
10. Tassigna ®
11. Tracleer ®
12. Trisenox ®
13. Xagrid ®
14. Zavesca ®

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