REGULATORY STRATEGIES AND PRACTICAL ASPECTS FOR THE DEVELOPMENT AND AUTHORISATION OF ORPHAN MEDICINAL PRODUCTS IN THE EUROPEAN UNION

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vorgelegt von
Dr. Matthias Dormeyer
aus Hagen

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Betreuer und 1. Referent: Markus Ambrosius
Zweiter Referent: Dr. Rembert Elbers

Experiences after more than 500 orphan medicinal product designations and nearly 50 authorized orphan drugs.

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ABBREVIATIONS

CCR	Complete clinical remission
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloic leukaemia
CNS	Central nervous system
COMP	Committee for Orphan Medicinal Products
CP	Centralized Procedure
CR	Complete remission
CV	Cardiovascular
DBP	Diastolic blood pressure
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
EC	European Commission
EEA	European Economic Area
EMEA	European Medicines Agency
EPAR	European Public Assessment Report
FVC	Forced vital capacity
GIST	Gastrointestinal stromal tumor
HCC	Hepatocellular carcinoma
HU	Hydroxyurea
INN	International Non-Proprietary Name
LoQ	List of questions
MA	Marketing authorisation
MR	Mutual recognition
MRCC	Metastatic renal cell carcinoma
MSDBP	Mean standing diastolic blood pressure
NA	Not applicable
NYHA	New York Heart Association
OMP	Orphan medicinal product
ORR	Overall response rate
PAH	Pulmonary arterial hypertension
PD	Pharmacodynamic
PEG	Paediatric Expert Group
PFS	Progression free survival
pINN	Proposed INN
PK	Pharmacokinetics

PR	Partial response
PSO	Public summary of opinion
RCC	Renal cell carcinoma
RMP	Risk management plan
SAWP	Scientific Advice Working Party
SCS	Sickle cell syndrome
SD	Standard deviation
SPC	Summary of product characteristics
TTP	Time to progression
VASPI	Visual analogue scale of pain intensity
WEU	Well established use

INTRODUCTION

The word orphan is derived from the Greek word ορφανοσ – a child who has lost one or both parents or a parent who has lost a child (Aronson, 2006). Whereas other words such as the German "Arbeit" (work) have similar etymological roots in modern English the word orphan is used in its original sense.

One general understanding of an orphan disease is that it described diseases neglected by doctors – orphan from the medicinal community. In a more strict sense, it designates diseases that affect only a small number of individuals. However there is no generally accepted definition of an epidemiological threshold for an orphan disease. In fact, in several countries and regions different legislations have been installed to support the development of orphan drugs. Interestingly, except for the European Union everywhere in the world the definition of rarity has been defined as total number of patients, e.g. with less than 200,000 cases in the USA. This means that with increasing population the prevalence of the disease decreases[1] [2]. In contrast, the criteria of orphan diseases in the EU comprise a prevalence of 5.0 per 10,000 or less (Aaronson et al., 2006). An overview of some characteristics of orphan legislation is summarized in Table 1.

Table 1: Epidemiologic thresholds of orphan diseases in various countries/regions.

Country/Region	Number of cases	Prevalence	Year of Legislation
USA	200,000	6.6 per 10,000*	1983
Japan	50,000	1.5 per 10,000*	1985
Australia	2,000	1.0 per 10,000*	1997
European Union	248,500#	5.0 per 10,000	2001
"World" (WHO definition)	4.3 – 6.6 mio#	<6.5 – 10 per 10,000	-

* calculated on the basis of the number of cases and population
\# calculated on the basis of the prevalence and population

The fact, that currently by far more than 500 products received orphan designation in the EU and nearly 50 orphan medicinal products are authorized clearly indicates that the incentives are regarded being a benefit. Overall approximately 8% of all designated products are marketed so far. Having in mind that the orphan regulation was established in 2001, the fact that many products receive designation during the early preclinical development, and the high attrition rate[3] it is adequate to conclude that the European orphan procedure is a success with regards to its aim to provide medicines for neglected diseases.

On the other hand, the currently available orphan products cover less than 40 orphan conditions and in many cases only a fraction of the patients will benefit from the drug. It is also frequently observed that these drugs do not enable full control or even cure of the diseases. Having this in mind as well as the fact that there is an estimated number of

[1] Prevalence of a disease is defined as the total number of cases of the disease in the population at a given time, or the total number of cases in the population, divided by the number of individuals in the population.

[2] To give an example, in 1990 there were 246 mio inhabitants in the USA corresponding to a threshold prevalence of 8.1 per 10,000. Today the population has increased by approximately one fifth resulting in a lower prevalence of 6.6 per 10,000.

[3] A rough approximation is that only 10% of all drugs that enter formal development will be authorized finally.

more than 5,000 rare diseases awaiting therapy makes clear that the development of orphan medicinal products is an important task for future (Joppi et al., 2006).

This thesis shall provide information and guidance to support the successful designation, development and authorisation of orphan medicinal products rather than providing an overview of the regulatory situation.

RESULTS

The overall results will be presented in four major subsections covering

- General and strategic considerations
- The designation process
- Peculiarities in the development of orphan medicinal products (OMP)
- Authorisation of OMP

GENERAL CONSIDERATIONS

The regulatory process for a marketing authorisation of an orphan drug in the EU is generally a two step process. In the first step a medicinal product is designated by the European Commission (following the opinion of the Committee for Orphan Medicinal Products – COMP) as being an orphan medicinal product. In a second step this investigational medicinal product has to be authorized as an orphan drug.

The designation can only be obtained prior to marketing authorisation in the orphan indication. Of course it is possible to authorize an already marketed product as an orphan drug in a new indication. One example for the latter case is sildenafil which is authorized under the trade name Viagra for the treatment of men with erectile dysfunction. Revatio (containing the same active ingredient) is an orphan medicinal product for the treatment of pulmonary arterial hypertension. The active ingredient is sildenafil. Authorisation holder of both products is Pfizer Ltd. The only difference is the strength of the film coated tablets (Revatio 20 mg, Viagra 25 -100 mg). Similarly, ibuprofen is not only a generically available non-steroidal anti-inflammatory drug, it is also authorized under the trade name Pedea for the treatment of patent *ductus arteriosus* in preterm newborns. In such cases a new marketing authorisation with a new brand name has to be submitted. It is not foreseen to extend an existing authorisation of non-orphan drugs to orphan conditions and take advantage of the orphan incentives.

Requirements for Orphan Medicinal Product Designations

Orphan Condition and Orphan Medicinal Products

According to regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 ("The Orphan Regulation"), the criteria for designation of an orphan medicinal product are (Article 3, 1.):

- that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition,
- that this condition affects no more than five in 10 thousand persons in the Community when the application is made,
- and 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.

An alternative to the prevalence threshold mentioned above is 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. However, there is no example for an authorized orphan medicinal product of this type and at most few single cases for such des-

ignations if at all. This approach represents an exception with no relevance in daily regulatory life and will not be pursued in this thesis.

In general, an orphan medicinal product has to be used for treatment, diagnosis, or prevention of a condition. Of 520 orphan designations, a total of 483 (corresponding to 93% refer to treatment, whereas only 33 are intended for prevention and 4 for diagnosis (June 2008). For this reason, the focus is set on treatment in this analysis. In particular the cases of prevention and diagnosis are also included but this is explicitly mentioned in those sections.

Pros and Cons for Orphan Drug Designation

The orphan process is not mandatory. In other words, it is the choice of the sponsor if a drug that fulfils the criteria according to Article 3.1 of the orphan regulation shall be authorized as a normal medicinal product or as an orphan drug. For example, multiple myeloma, a B-cell derived malignancy, is a recognized orphan disease. In 2004 Velcade (INN bortezomid) was authorized under exceptional circumstances for the treatment of this disease but not as an orphan drug. On the other hand, in 2007 and 2008 Revlimid and Thalidomide Pharmion were authorized for this condition as orphan drugs. Similarly, MabCampath was authorized in 2001 for the treatment of chronic lymphocytic leukaemia (CLL) – a well recognized orphan disease. Also, a negative opinion during the orphan designation process has no influence on the authorisation as a "normal" medicinal product. For example ^{90}Y-radiolabeled ibritumomab tuixetan is authorized in the treatment of B-cell non-Hodgkin lymphoma under the trade name Zevalin despite the fact that a prior negative opinion during the orphan designation procedure was obtained.

Orphan designation offers several advantages for the applicant but also potential disadvantages. These will be discussed in more detail in the section below.

Advantages of Orphan Medicinal Product Designation

The orphan drug status offers some benefits for the sponsor during development of the medicinal product as well as during marketing authorisation[4]. These comprise:

- Free scientific advice (called protocol assistance)
- Reduction of fees during authorisation
- Market exclusivity
- Funding and national incentives
- Public relations and credibility

Scientific advice (called protocol assistance for orphan medicinal products) at the EMEA is a highly recognized support for the development of medicinal products in the EU. This important procedure is offered for free for sponsors of OMPs. This incentive is quite substantial as fees for scientific advice are in the range of 36,400 to 72,800 Euro.

Another incentive for orphan medicinal products is fee reduction.[5] [6] OMP receive a 50% reduction of all fees for new applications of marketing authorisation. For products authorized under the centralized procedure such reduction is substantial as the basic fees amount 242,600 € (as of April 2008). In addition, pre-authorisation inspections are eligible for a complete fee exemption. In the first year after grating of a marketing authorisation

[4] As laid down in Articles 6 to 9 of the Orphan Regulation.

[5] In fact, free protocol assistance is also a kind of fee reduction.

[6] Described in detail in the "EMEA Public Statement on Fee Reductions for Designated Orphan Medicinal Products" (EMEA-H-404-01-Rev.7, 18 December 2006), www.emea.europa.eu/pdfs/human/comp/404201.pdf

post-authorisation activities is also reduced by 50% but this incentive is restricted to small and medium size enterprises.

Following authorisation of orphan medicinal products market exclusivity is granted for the product in the authorized orphan indication. This protection covers not only the authorized product but also similar compounds[7]. Another advantage of this kind of protection is that it is monitored by the EMEA rather than the authorisation holder as for instance required in cases of violation of patent protection. A more detailed analysis of the market exclusivity will be presented in the following section.

Several additional financial incentives are granted to Sponsors of OMP[8]. This includes also to European funding. The currently ongoing European Union's Seventh Framework Program for Research and Technological Development (FP7, 2007 – 2013) shall in particular support the research into rare diseases (for details please see www.codis.lu) However, it should be noted that designation does not automatically qualify for EU funding rather than particular projects and programs being created to support such work. In addition, there are also particular national incentives: Similar to the EMEA several countries offer free scientific advice (e.g. Denmark, Finland, Netherlands). In other countries OMP are directly qualified for reimbursement or reimbursement negotiations are simplified (e.g. Italy). Some countries, such as France or The Netherlands, also offer tax incentives for sponsors of OMPs.

Last but not least, such orphan designation has a good reputation among investors. This is most likely due to the marked exclusivity foreseen for orphan drugs. Another recognized factor is that orphan designation requires initial analysis of the projects. This means for investors that these projects have already been reviewed by an expert panel and the plausibility of the therapeutic approach has been sufficiently justified. Such advantage appears to be of particular interest of small biotech companies that depend on venture capital and other investors.

Marketing Exclusivity and Similarity

A ten year marketing exclusivity is granted for the use of the medicinal product in the orphan indication. This covers not only the active substance itself but also "similar products". The relevance of the similarity claim for orphan medicinal products will be summarized in the second part of this section.

This marketing exclusivity is frequently misunderstood: The perception that this protection refers to treatment of the orphan condition is widespread. However, this is essentially not true. This can be seen from the fact that there a several OMPs authorized in the last years for the same indication - in fact even similar or same indications.

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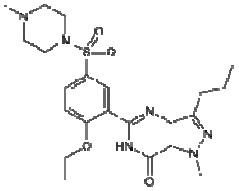
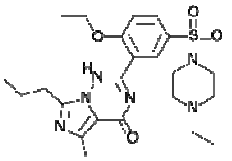
[7] As will be discussed in more detail sildenafil – Viagra – is authorized as an orphan drug for the treatment of pulmonary arterial hypertension (PAH) under the trade name Revatio. Whereas vardenafil (Levitra) was authorized in the treatment of erectile dysfunction an authorisation as an orphan drug in the same indication as sildenafil appears very unlikely due to the high level of similarity.



Sildenafil



Vardenafil

[8] See "Inventory of Community and Member States' incentive measures to aid research, marketing development and availability of orphan medicinal products", revision 2005 http:ec.europa.eu/enterprise/pharmaceuticals/orphanmp/doc/inventory_2006-08.pdf.

Details on the marketing exclusivity are defined in the Commission Regulation (EC) 847/2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts "similar medicinal product" and "clinical superiority". "Similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in a currently authorized orphan medicinal product, and which is intended for the same therapeutic indication. "Similar active substance" means an "*identical active substance, or an active substance with the same principal molecular structural features (but not necessarily all of the same molecular structural features) and which acts via the same mechanism*". Accordingly, an identical mode of action is a necessary prerequisite for similarity. In reverse the fact that both prerequisites are linked by the Boolean operator "and" has an important implication: A (non-identical) compound with the same structural features but with a different mode of action is not similar.[9]

Depending if the active substance is a small molecule, a radiotherapeutic or a macromolecule (such as a protein drug) different structural features are regarded being similar:

- **Small molecules:** isomers, mixture of isomers, complexes, esters, salts and non-covalent derivatives of the original active substance, or an active substance that differs from the original active substance only with respect to minor changes in the molecular structure, such as a structural analogue.
- **Proteinaceous substances:**
  - with a difference is due to infidelity of transcription or translation
  - with difference in the amino acid sequence is not major[10]
  - monoclonal antibodies bind to the same target epitope
- **Polysaccharide substances** having identical saccharide repeating units, even if the number of units varies and even if there are post-polymerisation modifications
- **Polynucleotide substances (including gene transfer and antisense substances):**
  - the difference in the nucleotide sequence is not major[11]
  - the difference in structure between them relates to modifications to the ribose or deoxyribose sugar backbone or to the replacement of the backbone by synthetic analogues
  - the difference is in the vector or transfer system
- **Radiopharmaceuticals** with the same radiopharmaceutical active substance, or one differing from the original in radionuclide, ligand, site of labelling or molecule-radionuclide coupling mechanism linking the molecule and radionuclide provided that it acts via the same mechanism

In addition it is stated that closely related complex partly definable substances (such as two related viral vaccines, or two related cell therapy products would be regarded similar. However, there has been no example so far for which this broad definition was applicable.

It should be noted, that the similarity claim is not applicable for products where a significant benefit compared to the authorized treatments can be demonstrated.[12] This is again clearly in the interest of the patients and of the fundamentals of the orphan regulation, requiring benefit over the available treatments.

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[9] This may sound like a theoretical construct but it should be kept in mind that similar compounds such as enantiomers can have entirely different biological properties, e.g. (R)-(+)-limonene smells orange-like and its enantiomer turpentine-like.

[10] Therefore, two pharmacologically related protein substances of the same group (for example, two biological compounds having the same INN sub-stem) would normally be considered similar

[11] For instance for antisense substances, the addition or deletion of nucleotide(s) not significantly affecting the kinetics of hybridisation to the target would normally be considered similar

[12] Regulation (EC) 141/2000, Art. 8, (3) c)

There are five interesting examples where several medicinal products were authorized for the treatment of a similar indication or where these treatments are falling under a common orphan condition. These are:

- Treatments for pulmonary arterial hypertension (PAH): Tracleer, Ventavis, Revatio, Thelin, Volibris
- Thalidomide and its analogue lenalidomide for the treatment of multiple myeloma
- Bcr-Abl protein kinase inhibitors for the treatment of (Philadelphia chromosome positive) chronic myeloic leukaemia (CML): Sprycel, Glivec and Tasigna
- Replacement therapy for Fabry disease: Replagal and Fabrazyme
- Treatments for renal cell carcinoma (RCC): Sutent, Nexavar and Torisel.

In all cases, the decision was that the succeeding medicinal products were not similar to the already authorized orphan medicinal products.

In fact, taken together similarity had to be estimated for a total of ten orphan medicinal products. It is interesting to note that despite the fact that it is expected that no major drug development would be expected without incentives a total of 15 orphan medicinal products (representing nearly a third of all OMPs) are authorized for the treatment of five orphan conditions only.

The most prominent example can be seen for the total of five medicinal products authorized for pulmonary arterial hypertension, a severe and often fatal disorder of the lung in which the pressure in the pulmonary artery is pathological increased. A summary is presented in the table below.

Table 2: Orphan medicinal products authorized for the treatment of pulmonary arterial hypertension.

Brand	Active Ingredient	Mode of Action	Therapeutic Indication[13]	MA Date
Tracleer	Bosentan	Endothelin receptor antagonist	Treatment of PAH to improve exercise capacity and symptoms in patients with grade III functional status.[14]	5/2002
Ventavis	Iloprost	Prostacyclin + prostaglandin E receptor agonist	Treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms.	9/2003
Revatio	Sildenafil	PDE V inhibition	Treatment of patients with PAH classified as WHO functional class III, to improve exercise capacity.	10/2005
Thelin	Sitaxentan sodium	Endothelin A receptor antagonist	Treatment of patients with PAH classified as WHO functional class III, to improve exercise capacity.	10/2006
Volibris	Ambrisentan	Endothelin receptor antagonist	Treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity (see section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease	4/2008

[13] This refers to the authorized indication rather than orphan condition.

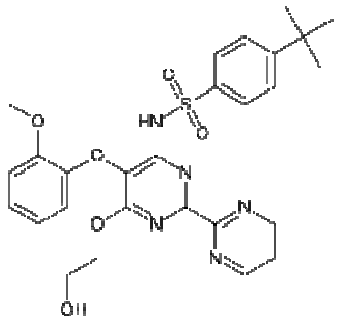
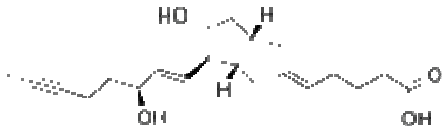
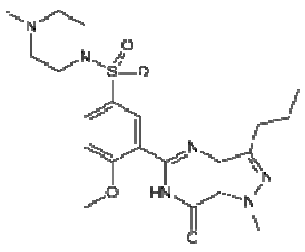
[14] In July 2008 the indication for Tracleer was extended to class II patients.

For all drugs that were authorized following the first authorized orphan product Tracleer the question of similarity was addressed during the authorisation procedure. In all cases the decision has been that the products were not similar:

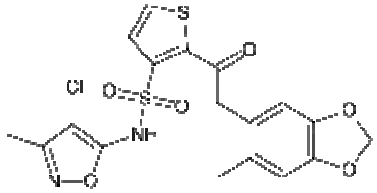
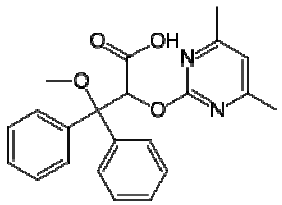
- For Ventavis no discussion of potential similarity is included into the EPAR but it has a different mode of action compared to Tracleer.
- For Revatio it is stated that the "*principle molecular structure feature and mechanism of action differ*" (EPAR)
- In the EPAR of Thelin it is laconically stated that it is not similar to Tracleer, Ventavis or Revatio. An appendix 1 is referenced that is not publically available. The mode of action is the same as for Tracleer but the structures differ clearly (see table below).
- Similarly, in the EPAR of Volibris it is stated that it is not similar to any of the other authorized treatments for PAH. The mode of action is the same as for Tracleer and Thelin but the structures differ.

An important factor is the questions if the mode of action is the same: Three of the PAH treatments act by inhibition of the endothelin system but the structures are clearly distinct as is obvious from the table below. In summary, none of these drugs is structurally related to each other justifying rejection of the similarity claim despite more or less identical therapeutic indications.

Table 3: Structures of authorized treatments for PAH[15]

Brand	**Active Substance**	**Structure**
Tracleer	Bosentan*	
Ventavis	Iloprost	
Revatio	Sildenafil	

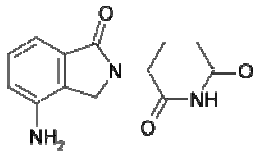
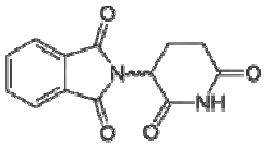
[15] Source of all structural formulas: Wikipedia

Thelin	Sitaxentan sodium*	
Volibris	Ambrisentan*	

* Endothelin receptor antagonists

Another interesting example which should be noted with regards to similarity and marketing exclusivity refer to the products Revlimid (lenalidomide) and Thalidomide Pharmion (thalidomide). For both marketing authorisation was granted for the treatment of multiple myeloma.[16] A comparison is presented in Table 4.

Table 4: Comparison between Revlimid and Thalidomide Pharmion

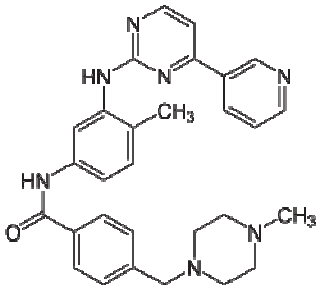
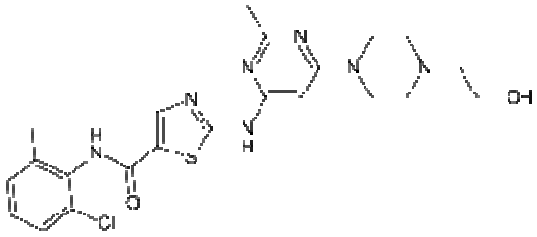
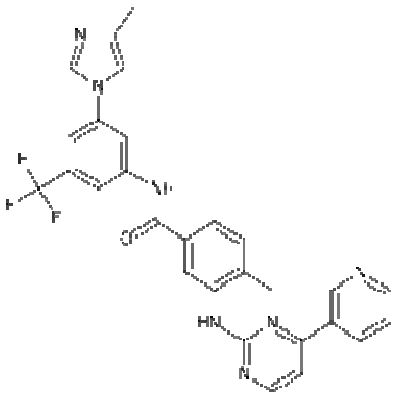
Brand	**Active Ingredient**	**Structure**	**Authorized Indication**
Revlimid	Lenalidomide		In combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy
Thalidomide Pharmion	Thalidomide		In combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.

It is obvious from the Table 4 that both drugs are structurally closely similar and are used for the treatment of the same condition (i.e. multiple myeloma). However, as they are not authorized for the same indication (roughly spoken treatment of patients who failed prior therapy versus first line treatment) the CHMP was of the opinion that the products are not similar. This fundamental decision is covered by the orphan regulation as it is stated in article 8, 1. that no marketing authorisation will be granted for products "*for the same therapeutic indication*". Such stipulation is clearly in the interest of the patients – as expressed in recital (2) and (8) of the orphan regulation - but not of the authorisation holder as the marketing exclusivity as one of the most important incentives for orphan medicinal products is significantly smaller compared to protection of the orphan condition.

[16] It is worth noting that there is another treatment authorized for therapy of multiple myeloma – but not as an orphan drug. Velcade (bortezomib, EU/1/04/274).

A third group of products comprises inhibitors of the brc-abl kinase for the treatment of chronic myeloic leukaemia (CML). This chimeric protein is formed as a consequence of a reciprocal translocation between chromosomes 9 and 22 resulting in the formation of the so-called Philadelphia chromosome that is present in 90% of all CML patients. In total three inhibitors this kinase are authorized with CML being the target condition.

Table 5: Inhibitors of the brc-abl kinase for CML treatment.

Brand	**Active Ingredient**	**Structure**	**Authorized Indication (CML only)**
Glivec	Imatinib		Treatment of: - adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment. - adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis.
Sprycel	Dasatinib		Treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate
Tasigna	Nilotinib		Treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib

In the analysis of a potential similarity of Sprycel the product is also compared to clofarabine (Evoltra) another orphan drug authorized for the treatment of CML. No similarity exists in this case which already evident from the fact that both products have different modes of action.

Interestingly, it is stated in the EPAR that Tasigna is similar to Glivec and not similar to Sprycel with regards to the molecular structure. In addition, the therapeutic indications for Sprycel and Tasigna are very similar and both are subsets of the indication authorized for Glivec. However, Tasigna is still authorized as "*the holder of marketing authorisation for Glivec has given his consent to the applicant*".[17] Tasigna is of clear benefit compared to Glivec as imatinib resistant or intolerant patients can be treated. In case of significant benefit of the succeeding project the market exclusivity can be derogated. For this reason, it appears that the consent by the authorisation holder would not have been required. On the other hand, Tasigna is not similar to Sprycel which is already authorized in the same condition justifying the authorisation in terms of similarity. But one might question if the justification for significant benefit was warranted in this case (this issue will be discussed in the section *The Significant Benefit Claim*).

This example allows estimating the thresholds of similarity in more detail as it is quantitatively assessed in this example. The CHMP simply compares the molecular weights of the identical fractions to quantify similarity: Tasigna and Glivec share a structural motive[18] of 53%/49% of the total molecular weight. In addition, both have in common a phenyl ring linked via an amide or inverse amide to the core moiety (if the phenyl moiety is included the identity is even increased to 82%/88%). As a conclusion it is stated that "*if a molecule is 50% identical with the possibility of even more additional similarity it is enough to conclude structural similarity*". Compared to that Tasigna and Sprycel share only 23%/27% or 17%/20% of their structure depending if only the pyrimidylamine or also the amide moiety linked via an aromatic residue are included[19]. If this principle is applied to thalidomide/lenalidomide an identical fraction of 84% becomes obvious which is in line with the conclusion that both products are similar. The two non-specific endothelin-receptor antagonists, bosentan and ambrisentan, share only the core pyrimidine moiety corresponding to 14%/20% of the molecular weight also confirming the above mentioned thresholds.

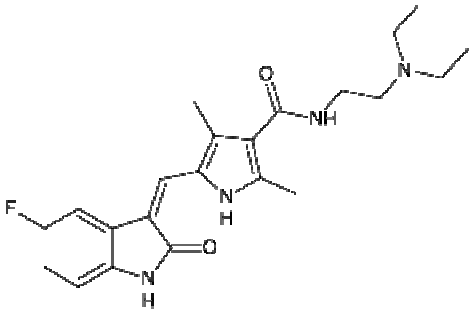
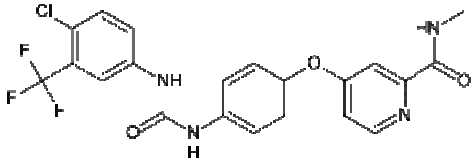
Another class of orphan compounds comprises treatments for renal cell carcinoma (RCC) in particular tyrosine kinase inhibitors authorized in this field. The kinase inhibitors are Sutent and Nexavar, whereas Torisel with the active ingredient temsirolimus acts by selective blockade of mTOR (a serine/threonine kinase). For this reason, despite the fact that the former treatments were already available when Torisel was authorized due to different modes of action similarity is no problem which is also supported by different mode of action. Sutent and Nexavar are compared in the table below in more detail.

[17] According to Article 8, 3(a) of regulation 141/2000 such procedure is allowed.

[18] N-(2-methylphenyl)-4(3-pyridinyl)-2-pyridinamine.

[19] In the EPAR an identity of 20%/22% is reported that is difficult to be reproduced.

Table 6: Comparison of Sutent and Nexavar in the treatment of RCC

Brand (Active Ingredient)	Targeted Kinases	Therapeutic Indication	Structure
Sutent (Sunitinib)	RAS/RAF/MEK/ ERK pathway c-KIT, FLT-3, PDGFR, VEGFR	Treatment of advanced and/or metastatic renal cell carcinoma (MRCC).	
Nexavar (Sorafenib)	c-KIT, FLT-3, PDGFR, VEGFR	Treatment of advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy	

Interestingly, as part of the EPAR similarity is only discussed for Sutent with regards to Glivec which is of course no problem as they are authorized in different disease areas (independent widely distinct kinase inhibition patterns and structural features). Most likely, the similarity was not discussed despite the fact that the indications and targeted kinases are widely overlapping as both medicinal products were authorized at the same time (CHMP Meeting, April 2006). However, as the structures are definitely distinct there should have been no problem in any case.

A particularly interesting example refers to replacement therapies in patients with Fabry disease, an X-linked recessive glycosphingolipd storage disorder caused by deficient activity of the lysosomal enzyme alpha galactosidase A: Replagal and Fabrazyme with the active ingredients agalsidase alpha and beta were the first orphan medicinal products being authorized in the European Union. Both procedures started on the very same day – 18 July 2000 – and the CHMP opinion was also adopted on the same day for both products. 3 August 2001. Nevertheless the example is dealing with two independent and self standing applications[20]. The EPARs do not contain any discussion of potential similarity which despite the act that both medicinal products are clearly similar: same INN sub-stem[21] and same authorized indication. Obviously, the CPMP dealt with the problem by simultaneous authorisation of Replagal and Fabrazyme. As orphan designation was also granted on the

[20] This obvious from different factors such as the different authorisation holders, different numbers of patients, different timelines with respect to response to questions, and the fact that Replagal is authorized under exceptional circumstances and Fabrazyme not.

[21] According to regulation 847/2000, article 3, (3) 2.1

same day (8 August 2000[22]) it appears that the sponsors of both projects had also agreed on a common procedure.

Peter Sattler has analysed the current experiences with potentially similar OMPs in much more detail in his MDRA Master Thesis "Assessment of potential similarity of orphan drugs" (2007). Unfortunately this thesis was not available but the summary of this thesis is attached in Annex IV.

Taken together according to the regulation 847/2000 and current experiences with medicinal products where potential similarity has been discussed during the authorisation procedure the following conclusions can be drawn with regards to market exclusivity:

1. Compounds with the same mode of action can be authorized in the same disease area if they are not structurally similar. In other words sharing the same mode of action is a necessary but not sufficient criterion for similarity.
2. In case two products have the same mode of action major structural differences are required to justify the assumption of similarity. It can be estimated on the basis of the molecular weight of identical structural moieties that if these represent less than 30% of the overall molecular weight similarity is unlikely, if they represent more than 50% - depending on other structural features - similarity becomes likely whereas above 80% both products are similar.
3. Similar products according to the specifications defined in Article 3 of the regulation 847/2000 can be authorized for the same orphan condition as long as the therapeutic indication is different.
4. In the event of a similar product is clinically superior to the initially authorized OMP the market exclusivity is not applicable.

In conclusion, the marketing protection granted for orphan medicinal products is not very comprehensive. Such protection covers the use of the medicinal product and similar products in the treatment of the authorized orphan indication. This means that a similar or even the same product can be authorized in the same condition if the indication is different (see for exemplification of the difference of indication and condition the above listed example with thalidomide/lenalidomide). Furthermore, in case a significant benefit of the new therapeutic agent can be demonstrated this also justifies authorisation of a new product that is regarded being similar according to the criteria defined above[23]. Accordingly, during estimation of potential revenues from the project after authorisation, the marketing exclusivity should not be overestimated. On the other hand, if one develops a product which might be similar to an already authorized orphan drug it might be possible to shift the clinical focus to indications that are not covered by the available product.

They may also be applications for innovative products that are patent protected where the patent comprises a broader "umbrella structure". In case the term of the patent is more than ten years at the time of authorisation such projects benefit of course less from the market exclusivity.

[22] Interestingly this date is shortly after start of the authorisation procedure. However at that time the positive opinion of the COMP was available: 11 July 2000.

[23] Interestingly, one could argue that it is not of relevance if the protection covers the orphan indication only or the orphan condition. If a (similar) product is used to treat another subpopulation of the orphan condition different to the currently targeted patients one could regard this as a significant benefit of this new therapeutic.

OMP and the Centralized Procedure

Authorisation via the centralized procedure is mandatory for orphan medicinal products[24]. The idea behind that is ensuring a drug that drug that is of benefit for few patients should be available for all patients. Such centralized authorisation does not mean that it also has to be marketed all over the European Economic Area. But the whole labelling has to be prepared accordingly (i.e. SPC, PIL and outer package have to be translated into all official languages of the EU).

There is no general consensus if it is an advantage or a disadvantage that the centralized procedure has to chosen. This depends of course on the product, the treated condition as well as on the company strategy. If for instance marketing in all countries is intended the centralized procedure is much cheaper than MRP/DCP in particular if the fee reduction granted to orphan applications is taken into consideration. If on the other hand the company aims only at marketing in few countries MRP/DCP might be a preferably way that cannot be chosen for orphan products.

It is not required to demonstrate that the product is eligible to the centralized procedure. Such products are automatically qualified. Still for formal reasons the eligibility request has to be submitted but it includes the form only.

Disadvantages of Orphan Medicinal Product Designation

There appears to be only one important (potential) disadvantages associated with orphan medicinal product designation. As soon as the European Commission decided that OMP designation will be granted to a particular project, a public summary of opinion (PSO) will be published on the EMEA homepage[25]. The PSO includes the exact name of the medicinal product (such as INN or chemical name). This can be a problem in case of new chemical entities where the structure is regarded confidential. The exact nature of the drug will therefore be obvious from the PSO. In such cases it is recommended to delay the designation process until the structure has become public or – in case this is not feasible – to the latest possible time point before submission of marketing authorisation is filed.

Timing of Designation

The sponsor may apply for designation of a medicinal product as an OMP at any stage of the development before the application for marketing authorisation is made.[26]

As will be outlined in the next section in much more details, the orphan designation procedure follows strict timelines. In addition most applications for designation are successful within this time frame resulting in a positive opinion by the COMP and favourable decision by the European Commission.

A general rule for the best timing of application for orphan designation cannot be made as this depends on various parameters, such as intellectual property situation and overall strategy of the company. For instance, some biotech companies aim at continuous press coverage. In such cases a designation process might be initiated to ensure that the COMP opinion can be obtained at a certain time period. In most cases, the uncertainty of predicting the timelines for such procedure is one month.

One still can say that designation can be envisaged as soon as prove of concept data from an animal disease model are available. Normally such information is sufficient to justify the medical plausibility of the approach. In fact, in some cases early clinical data make

[24] Regulation 726/2004, Point 4 of the Annex.

[25] http://www.emea.europa.eu/htms/human/orphans/opinions.htm

[26] Regulation (EC) 847/2000, Article 2, 4.(a)

the designation process more difficult. For instance is frequently seen that early phase II data are not well-defined and unambiguous. Another issue might be that PK data from phase I trials might lead to discussions if PK/PD modelling on the basis of animal data support the assumption of efficacy.

Another important factor that should be kept in mind refers to confidentiality. If the structure of a new active substance is regarded being confidential the designation should be rescheduled till the time when it not any longer regarded critical if the molecular formula becomes public. This is due to the fact that the Public Summary of Opinion published after successful designation contains exact information on the structural nature of the product.

Relevant Aspects for the Decision on an Orphan Strategy

There is no general overall strategy if or when to apply for orphan designation. There appears to be no global drawback associated with an orphan procedure. The major disadvantage of publishing a potentially confidential structure can easily be avoided by initiating the orphan procedure shortly before the submission of a marketing authorisation request (but of course early enough to ensure sufficient time for the whole procedure). Such approach is adequate as after the authorisation the structure will be published anyway.

As outlined in one of the previous sections there are programs which might not benefit too much from the orphan incentives. This is in particular true for products that are comprehensively and long-lasting protected by patents. On the other hand, there are also projects which might depend critically on such procedure. For instance, in case there is no patent covering this particular project, the marketing exclusivity might be important to ensure proper protection. Another important factor is if designation is required to convince (or even satisfy) investors.

Table 7 summarizes some relevant questions and potential implications and consequences for a potential orphan strategy.

Table 7: Some questions with potential relevance for the definition of an orphan drug development strategy.

Question	Yes	No
Is the product intended for the treatment of an orphan condition?	Orphan designation is possible	No orphan procedure possible. One might think if the product could also be used in an orphan condition and shift the development focus
Has medical plausibility been sufficiently demonstrated?	Orphan designation is possible at any time	Postpone application until sufficient data are available.
Is the project sufficiently protected by patent applications?	Depending on the scope and the term of patent protection the incentives are variable	Orphan drug status of major importance for protection of the product.
Is the structure of the product under development regarded confidential?	Designation should be postponed to a time point shortly before initiation of the authorisation procedure	Orphan designation is possible at any time
Is it intended to seek for scientific advice at the EMEA?	Prior orphan designation is recommended to take advantage of financial incentives	Orphan designation is irrelevant for this particular question

However, the table comprises only a selection of potential aspects that might contribute to the overall decision on an orphan designation strategy. Project- and company oriented features have always to be taken into consideration.

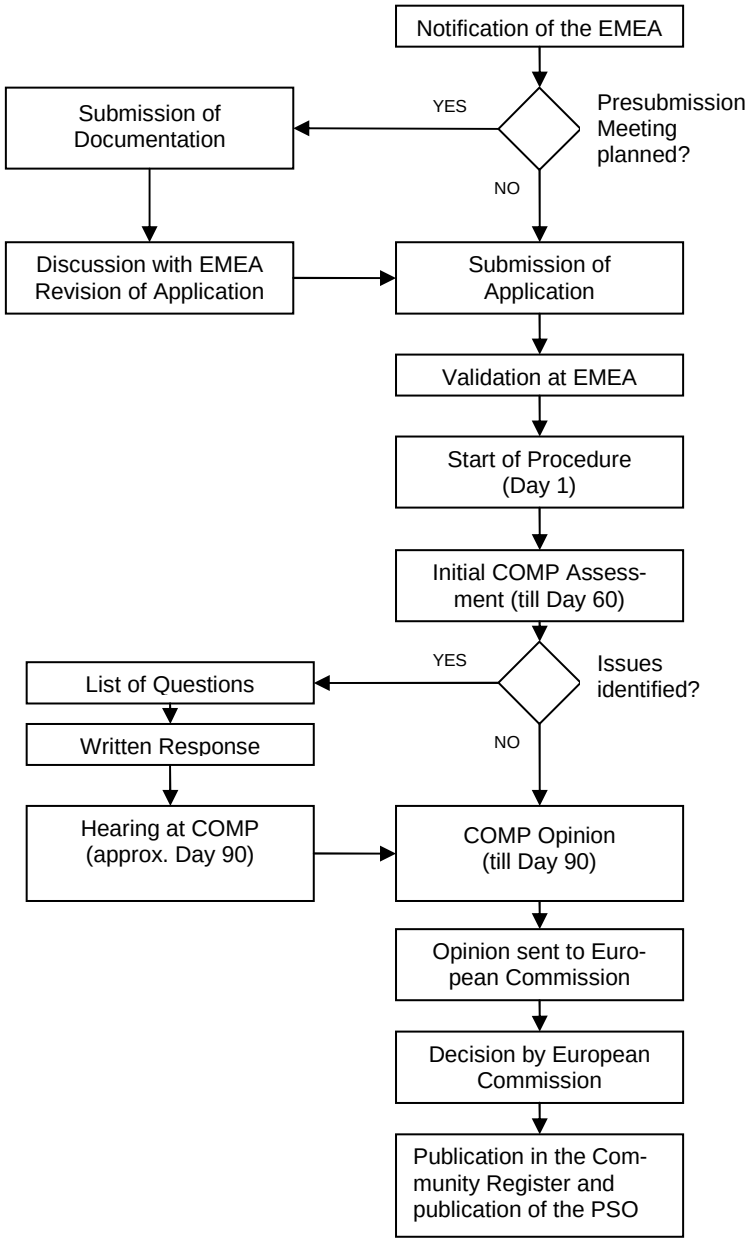
THE DESIGNATION PROCESS

As mentioned above, prior to authorisation as an orphan medicinal product designation has to be obtained. This follows a clearly defined procedure including a validation phase at the EMEA and afterwards a 90 day assessment by the Committee on Orphan Medicinal Products (COMP) resulting in a positive or negative opinion. In a subsequent 30 day period the European Commission converts the opinion into a decision that is legally binding and will be published.

In this section, the overall process will be outlined, critical issues will be identified and several recommendations will be presented to support a smooth overall designation procedure.

Procedural Aspects of the Designation Process

The procedure of orphan designation is presented in the flowchart below.



There are some important time points for the sponsor that will be presented and discussed in more detail in the following sections.

Notification to the EMEA

Notification to the EMEA that should be submitted at least two months prior submission. This can be done by means of an informal email or fax message stating product, condition and planned submission date and name and address of the sponsor. It should be noted that this is not a *conditio sine qua non* for submission of an orphan designation application rather than a request to allow the EMEA and COMP proper planning of the work. The request for notification is not included in the orphan regulation and the Commission Guideline states that the notification should be performed two months prior to submission "where possible". However, as part of good regulatory practice it is strongly recommended to follow this procedure.

Submission of the Application

The submission deadlines are fixed and the dates are presented on the EMEA website.[27] In most cases the submission deadline is approximately two weeks prior to the next COMP meeting. This time is required for validation and resolving potential issues identified.

The application package comprises the following documentation:

- Application (with original signature)
- Scientific Part of the Application (section A – F)
- Copies of all references
- Proof of establishment in the EU/EEA (e.g. copy of identity card or for companies a copy the commercial register entry)
- List of translations into all official languages of the EU (including the name of the product and the orphan condition including if the product is intended for treatment, prevention or diagnosis)

One original copy (signed and dated) and two additional copies of the application in electronic form (on 2 CD-ROMs) have to be submitted to the EMEA (European Medicines Agency, Scientific Advice and Orphan Drug Sector, 7 Westferry Circus, Canary Wharf, London, E14 4HB).

Validation at the EMEA

Upon submission the package is validated at the EMEA. This is typically achieved within one week. Accordingly, in case there are some validation issues there is in most cases approximately ten days time for the sponsor to revise and resubmit the application. In normal cases this time is sufficient to adjust the application accordingly. It will be outlined below in more detail that issues during validation frequently arise. For this reason it is recommended to ensure that key personal is available at the time the validation feedback is expected.

In the event that there are no issues the sponsor will obtain a tabular overview of the dates of the further procedure. In case there are validation issues the sponsor will receive an email or fax message where these issues are listed.

It is a common experience that during this first review not only formal aspects will be addressed but also issues with regards to the content of the application might be raised (e.g. definition of the condition or validity of the prevalence estimation). In some cases the ap-

[27] http://www.emea.europa.eu/htms/human/orphans/guidance.htm

plicant might not want to follow the requests for modification requested by the EMEA scientific administrator. In this case one should contact the EMEA coordinator directly and explain the position. According to our experience, it is dependent on the EMEA employee if the procedure goes on if there is disagreement with regards to questions of content or not. Some of them realize that they should not withhold the procedure as finally the opinion of the COMP is of relevance, whereas others insist in their position and refuse to validate the application. In the latter case (which luckily does not frequently occur) there appears only to be the possibility to transfer the discussion to the next administrative level at the EMEA in case one does not want to follow the suggestion for modification.

However, it should be noted that most of the EMEA Scientific Administrators have pronounced experience with orphan designations and have attended many COMP meetings. For this reason, issues raised during validation that concern the content of an application should be taken seriously as these might also be questions of interest for the COMP.

There is the possibility to have a pre-submission meeting with the EMEA[28]. This is typically a telephone conference. The sponsor is asked to submit the documentation package approximately two months prior to the meeting albeit shorter timelines are also feasible. This quite long period might be a disadvantage in case timelines are tight as this time has to added to the overall duration of the procedure. On the other hand, such pre-submission meetings significantly increase the probability of a successful validation without any issues (see below). For this reason if time is not critical one might think about having such a meeting.

The documentation that has to be submitted at least one week prior to the meeting date should contain the following:

- Draft of the application (full document, copies of the references not requested)
- A list of questions
- A short power point presentation about the application (approx. 15 min, including condition, product and development stage)
- List of participants
- Dialing number and password for conference

It should be noted that this procedure is strongly recommended by the EMEA. It will be outlined below that recent experience clearly shows that such pre-submission meetings significantly improve the probability of successful validation of the initial application. On the other hand, strategic aspects should be considered. Such process takes several weeks to a few months that have to be added to the overall timelines. On the other hand most validation issues can be resolved within the time between feedback and start of procedure. Accordingly, in the event that time is no major issue it is recommended to perform such procedure.

Assessment by COMP and Adoption of Opinion

Upon completion of validation and start of the procedure, the sponsor will receive a timetable containing the dates of the further procedure.

A valid application is reviewed and assessed by the COMP following a defined 90 day procedure[29]. This initial assessment is done by a COMP member who prepares and circulates a summary report within 47 days. Within one week comments on this report should be presented. During the next COMP meeting (that takes place approximately 60 days after start of the procedure), the application will be discussed. In case there are no issues a positive opinion can be granted during this session. Such an opinion should be based on

[28] See also "Practical information for sponsors during the early phase of an orphan drug application", EMEA/357465/2008/Rev 3, 24 June 2008

[29] Article 4, regulation (EC) 141/2000

consensus or at least a majority of two thirds. Typically within two days after the COMP meeting, a press released is published. In many cases this is prior to the formal notification of the sponsor about the positive opinion. For this reason the EMEA website should be consulted to see the press release as early as possible.

In case no positive opinion is mentioned in this press release the sponsor should be prepared to receive a list of questions comprising the issues raised by the COMP. This will be provided within a few days after the COMP meeting. Normally the sponsor is requested to present written responses within approximately 10 days. This timeline is not legally defined, but rather is determined by the EMEA and is to a certain degree negotiable. In parallel the sponsor is invited to present his opinion or additional data during the next COMP meeting. One should not expect that the written response is sufficient to clarify all issues and that the hearing will be cancelled. This is simply due to the case that no COMP meeting takes place between compiling the list of questions and the scheduled hearing. Accordingly, there is no possibility for the COMP to adopt an opinion substantially prior to the day 90 meeting. For this reason the sponsor should prepare for the hearing as soon as he is informed about the date. The date for the meeting is fixed and cannot be changed. It is therefore strongly recommended to ensure that all key people are available at the date of the Day 90 COMP meeting as soon as the timetable for the procedure is obtained.

It sometimes happens that the written response was sufficient to clarify all issues. Typically in such cases the sponsor travels to the EMEA where the meeting takes place and is informed prior to the hearing that a positive opinion has been issued. This can happen in fact as often as in every fifth case when a list of questions was issued by the COMP (see below).

If such hearing takes place the sponsor is requested to bring 50 printed copies of the slides as handouts for the COMP members. For convenience these should be handed to the EMEA one or two hours prior to the meeting. The sponsor should also inform the EMEA in advance about the facilities needed for presentation. A Power Point presentation is recommended. In such case a CD containing the presentation only should be prepared and left with the already mentioned copies. For safety reasons we would also recommend to have an additional copy prepared on a memory stick.

The overall time of the hearing is 50 minutes including a 20 minute presentation by the sponsor. The presentation should comprise a brief introduction into the project but particular focus should be set on the issues raised by the COMP. Potential open questions will be discussed afterwards. It is not seldom that also questions will be addressed that were not included into the written list Following the hearing the COMP will adopt an opinion (preferably consensus or at least with a two third majority). After the meeting the sponsor should wait in the lobby of the EMEA. He will be informed about the opinion of the COMP shortly after the hearing on the same day.

If it turns out during the meeting that the designation will not be supported by the COMP the sponsor will get the possibility to withdraw the application to avoid a public negative opinion. No information concerning such withdrawn applications will be published in such cases.

In case of negative opinion the sponsor may start an appeal process. However, it is strongly recommended to withdraw the application as outlined. The sponsor has the possibility to rework the applications taking the comments of the COMP into consideration and resubmit an application for the same product. On the other hand, during the appeal process the sponsor would start the discussion on the basis of the same data that led to a negative opinion in the COMP meeting. If it was not possible to convince the COMP during the hearing it is questionable of the appeal would lead to success. In addition, a negative outcome results in the publication of this negative opinion. Compared to that, a resubmission should be preferred. In this case the sponsor has the chance to start a new procedure, potentially at a later time with more convincing data. Such approach is some more time consuming than an appeal process but avoids in any case the publication of a

negative opinion, it is less conflict laden and allows the adjustment according to more flexible timelines. For this reason the appeal procedure will not be presented in more detail.

Procedure Following the Adoption of an Opinion

The opinion of the COMP will be forwarded to the European Commission (EC) and the sponsor. On the basis of the COMP opinion the Commission will adopt a decision within 30 days. Although in theory a negative Commission decision on the basis of a positive COMP opinion can be imagined this is only a theoretical concern as so far the EC always followed the opinion of the COMP.

The Commission decision will be published in the next press release of the COMP (which is approximately 60 days after the opinion). The sponsor will also receive a formal statement of the decision in all official languages of the EU.

The project will then be included into the Community Register of Orphan Medicinal Products[30]. In addition, a Public Summary of Opinion (PSO) will be published[31]. The sponsor will receive prior to publication a draft version to ensure that it will contain no confidential information. In rare occasions the draft contains mistakes with regards to content. For this reason it should carefully be reviewed.

Practical Aspects on the Designation Application

In this section some practical aspects with regards to drafting an orphan designation application will be presented.

Structure of the Application

The structure of an application for orphan medicinal product designation is defined in the Commission guideline ENTR/6283/00 Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another (Rev. 3 July 2007). An overview of the structure of the application is presented in Table 8 as well as some general comments.

Table 8: Structure of an OMP designation application

A	**Description of the condition**	
A1	Details of the condition	This is a section with text-book character: The disease should be clearly and comprehensively described
A2	Proposed orphan indication	Statement of the orphan condition. In case a subset is chosen it appears appropriate to include a justification here
A3	Medical Plausibility	One of the most critical sections of the application. The rationale and the scientific basis of the project should be obvious from this section
A4	Justification of the life-threatening or debilitating nature of the condition	An important but in most cases uncritical section of the designation: Provide data on patient survival and/or severe disablements caused by the condition.

[30] http://www.emea.europa.eu/htms/human/orphans/intro.htm

[31] List of PSO: http://www.emea.europa.eu/htms/human/orphans/opinions.htm

B	**Prevalence of the condition**	
B1	Prevalence of the orphan disease or condition in the Community	Very important section that should be drafted with great accuracy. Comprehensive research of the data and proper analysis is highly recommended.
B2	Prevalence and incidence of the condition in the Community	The heading might be misleading: This section is only applicable if designation is sought for treatment of a disease where without incentives, it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return on investment (see section C). For all applications arguing with an orphan disease with prevalence below 5 per 10,000 this section is not applicable.
B3	Information on participation in other Community projects	Data can be derived from www.cordis.lu Information should be included if the company receives funding from the European Union
C	Potential for return on investment	For designations of medicinal products In general, the section is not applicable if designation is based on a prevalence below 5 per 10,000. This approach is not covered by this study as its relevance is negligible.
D	**Existence of other methods of diagnosis, prevention or treatment**	
D1	Details of any existing diagnosis, prevention or treatment methods	All methods should be described, irrespective whether they are pharmacological or non-pharmacological methods.
D2	Justification as to why methods are not satisfactory	This section is only applicable if there are no authorized medicinal product for the treatment of the condition available in the EU, i.e. if there are only products available used off-label or non-pharmacological treatments Only either this section or D3 are applicable.
D3	Justification of significant benefit	This section is only applicable if there are authorized medicinal products for the treatment of the condition available in the EU. Only either this section or D2 are applicable. Section D3 is one of the most critical sections of an orphan designation application.
E	**Description of the stage of development**	
E1	Summary of the development of the product	An overview of the current development status of the project should be presented, covering brief summaries of chemical/pharmaceutical properties, non-clinical and clinical data including information from the development in other disease areas.
E2	Details of current regulatory status and marketing history	A brief overview is normally sufficient: Authorisation status and information on orphan designation in other countries
F	Bibliography	The preferred format for cross-referencing published literature is by the lead author and year e.g (Smith *et al*, 2002)

Most critical or important sections and aspects will be discussed in more detail below. This discussion will also comprise recommendations for successfully drafting the application.

As a rule of thumb the author should keep in mind that the application should clearly demonstrate that

- the condition of interest is an orphan condition (i.e. rare and serious without adequate treatment options)
- the medicinal product of interest is efficacious in the treatment of the orphan condition and is likely to provide benefit for the affected patients

Orphan Condition

Defining the orphan condition is not as trivial as it might appear on the first glance. Due to the fact that this is an important problem in the designation process and one of the most frequent reasons for rejection of an application this issue shall be outlined in more detail.

The Commission Guideline on content and format of OMP applications states that "*recognised distinct medical entities would generally be considered as valid conditions. Such entities would generally be defined in terms of their specific characteristics, e.g. pathophysiological, histopathological, clinical characteristics*"[32].

A particular problem is due to applications aiming at subsets of diseases. The designation process for such subsets is in general challenging. The Commission Guideline states that "*convincing arguments would need to be presented to justify the medical plausibility of any proposed subset and the rationale excluding the larger population. A subset of a disease […] could be considered a valid condition if patients in that subset present distinct and unique with a plausible link to the condition and if such characteristics are essential for the medical product to carry out its action In particular the pathophysiological characteristics associated with this subsets should be closely linked to the pharmacological action of the medicinal product in such a way that the absence of these characteristics will render the product ineffective in the rest of the population*". This position of the EMEA/COMP is due to the fact that it shall be avoided that an application defines a subset of a disease to gain the orphan incentives with a product which in reality for treatment of the broader condition.

The problems with definition of a subset shall be clarified by means of an imaginary example (which is for demonstration purposes slightly overdrawn): A new product for the treatment of severe acne during puberty shall be developed as an orphan drug. This condition is by definition a severe disease[33]. In addition, pubescent adolescents represent no more than 5% of the general population (one could say the prevalence of puberty is 500 in 10,000 at most. Taking into account that approximately 85% develop acne and assuming that only 1% is sever acne would result in an overall prevalence of 4.3 per 10.000 which is below the orphan threshold. Despite the fact that the disease is severe and rare and cannot be treated appropriately – although there are authorized therapies severe acne still exists – it would most likely not be accepted being an orphan condition. This is due to the fact that such product would raise the suspicion that it is intended for the treatment of acne in general, including acne in adults or milder forms and not only severe acne.

It will be shown below in more detail that applications with an invalid targeted subset of the condition is by far the most frequent reason for rejection of an orphan designation application. For instance there have been several examples where orphan designations were sought for products intended for the treatment of melanoma. Melanoma is not an orphan disease due to its prevalence so it is tempting to define subgroups. One possibility could be to define a subgroup on the basis of the thickness with a threshold of 0.75 mm (as it is agreed that this is a negative prognostic factor). Such approaches will most likely

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[32] ENTR/6283/00 Rev 2, page 7.

[33] The severity is also accepted by regulatory authorities as drugs containing isotretinoin (e.g. Roaccutane®) are authorized in this indication despite the fact that they have serious safety issues, including very frequently occurring anaemia or elevation of liver enzymes. The product is furthermore teratogenic. Such safety risks can only be justified in the treatment of severe diseases.

not be endorsed by the COMP. Thresholds defined in a continuous measure are always to a certain extent arbitrary. One can questions if the drug intended in this example is not active in the treatment of melanoma with a thickness of 0.7 mm or if surgical removal is impossible for lesions of 0.8 mm. Similar considerations can be made with regards to treatment efficacy, etc.

This does not mean that such applications are not possible, but typically such applications are much more difficult. There are in fact several examples where subsets are recognized orphan conditions, such as

- B-cell chronic lymphocytic leukaemia (this is a borderline case, but chronic lymphocytic leukaemia is also recognized being an orphan condition)
- Emphysema secondary to α1-antitrypsin deficiency (rather than emphysema in general. These designations refer to α1-proteinase replacement therapy).
- Ep-CAM-positive squamous cell carcinoma of head and neck (the designation refers to an Ep-CAM binding protein)
- Cutaneous forms of lupus erythematosus (using a topical formulation)
- Moderate and severe traumatic brain injury (rather than traumatic brain injury in general)

The latter is of particular interest as it is defined in the Commission Guideline (ENTR/6283/00 Rev 2) that different degrees of severity or stages would generally not be considered as distinct conditions. In other words, diseases such as stage IV melanoma or severe Alzheimer's disease are not regarded being valid conditions in the context of the orphan designation process. The reasons are the same as outlined above. The example of traumatic brain injury is clearly an exception to this rule. However, from a scientific point the rational behind this is plausible: Severe (closed) head injuries resulting in swelling or bleeding of brain tissue are clearly distinct from a mild concussion with regards to pathophysiology, histopathology, clinical characteristics and prognosis. Still, it is strongly discouraged to pursue such strategies as the experience shows that in most cases these applications are not successful. In fact, in case the applicant is of the opinion that in the particular case a stage or severity degree represents a distinct condition, prior discussion with the EMEA should be sought.

If the application of a subset is intended it should be clearly demonstrated that no activity in the broader patient population can be expected. With regards to the requests of the COMP to justify a subset, the examples listed above clearly fulfil these criteria, e.g. an EpCAM-binding protein is for evident reasons inactive in the treatment of EpCAM negative malignancies. Similarly, compounds counteracting cerebral oedema might be effective in the treatment of severe traumatic brain injury ("brain swelling"), but should not be of benefit in the treatment of mild forms, i.e. concussion.

In general, the fact that a subset of patients exists where the product is expected to have a positive risk/benefit ratio is regarded not to be sufficient to define the subgroup of a disease. Following what has been said above it should also be included to demonstrate that this specific efficacy is due to characteristics of the pathology in this subset. Such reasoning must result in the fact that the product is ineffective in the treatment of patients suffering from the broader condition.

As already mentioned there are some examples for not-accepted subsets of diseases. These include for instance:

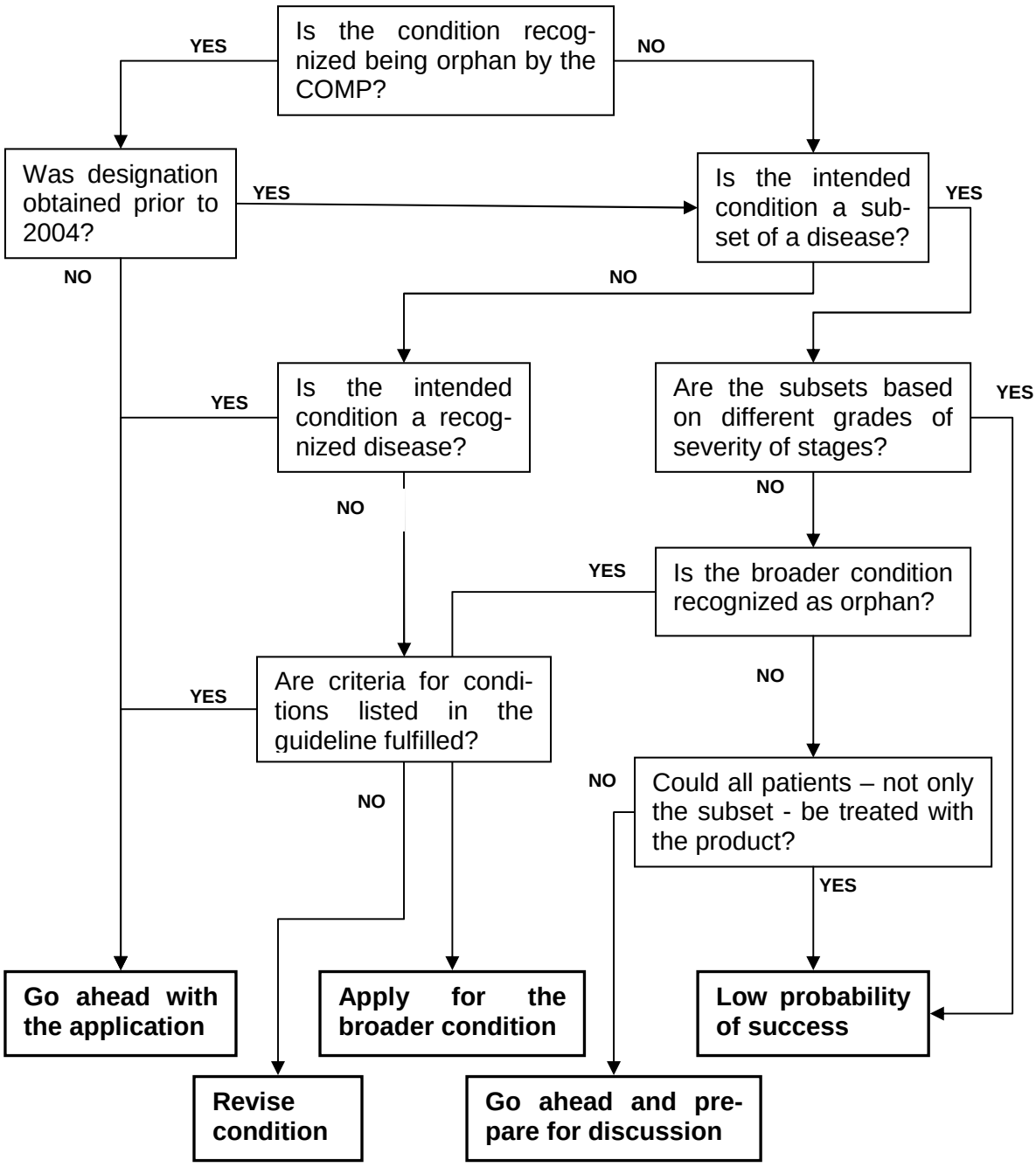
- Superficial bladder cancer (broader condition: bladder cancer)
- Painful HIV-associated neuropathy (broader condition: peripheral neuropathy)
- B-cell non-Hodgkin lymphoma (broader condition: non-Hodgkin lymphoma)
- Active phase of Peyronie's disease (broader condition: Peyronie's disease)
- Metastating malignant melanoma (broader condition: malignant melanoma)

For this reason it is strongly recommended to initially check if the disease is recognized as an orphan condition by the EMEA.[34] This can easily be achieved using the list of "summaries of opinion on orphan designation" published on the EMEA website[35]. However, it should be noted that there is no guarantee that such an approach will be successful. This is due to two reasons in particular. First, in some cases the discussion on the condition is not without controversy and if the composition of the COMP changes a shift in perception might also result. Secondly, in particular in the first years after the orphan regulation came into effect some opinions were adopted that are would probably not be supported by most of the COMP members today. For instance instead of "high grade glioma" it would be preferred today to use "glioma" as an orphan condition (in particular as glioma is also an orphan condition). But in most instances not major issues should be expected if the application refers to the treatment of a recognized orphan condition. Still all difference aspects (such as prevalence, reasoning of the life-threatening or severely disabling nature of the disease should be comprehensively described in the application as each document has to be self-standing.

It should be noted that there is no generally accepted criterion when a disease is regarded being a valid condition. According to Rembert Elbers (German COMP member, personal communication) a good rule of thumb is to ask if the condition was known as such before the development of the product was initiated. Helpful aspects are if the disease has an ICD code or simply if reviews or textbook chapters are dealing specifically with this condition are available.

In conclusion, proper definition of the condition is of importance for successful and smooth orphan medicinal product designation. Prior to drafting the application in particular the aspect should be carefully analysed if it is aimed at the treatment of a recognized (orphan) disease or at the treatment of a disease subset only. Whereas in the former case no major discussion with regards to the condition should be expected, in the latter case one should anticipate and be prepared for challenging discussions. The attached flow-chart on the next page shall support the definition of the condition of interest.

[34] In fact, there are two negative opinions each for superficial bladder cancer and painful HIV-associated neuropathy. In these cases initial check of the list of designations had been very helpful.
[35] http://www.emea.europa.eu/htms/human/orphans/opinions.htm



The Medicinal Product and its Active Ingredient

The product intended for the treatment has to be a medicinal product. The orphan procedure is not applicable to medical devices, diets, etc. In case tissue or cell derived products are used, it might be appropriate to perform a regulatory classification prior to filing the application. Such procedure is done by the Inovation Task Force.[36]

[36] The request form can be found under: http://www.emea.europa.eu/pdfs/human/itf/Regulatory%20Classification%20Request%20Form%afEMEA-6276-04-Final.doc

Information on route of administration and pharmaceutical form and its strengths should be provided wherever possible. This is of particular importance in cases where the product justifies the definition of a subgroup of a condition (see for instance above: the use of a topical product for the treatment of cutaneous forms of lupus erythematosus).

A simple formal request is to use the INN[37] during the designation process. In case there is no INN available, in the following order of priority the Ph.Eur. name, national pharmacopoeia name, common name, or scientific name should be chosen. For new products under development frequently the chemical name has to be chosen. As already mentioned, this name will be published which could be an issue if the structure is regarded confidential. Laboratory codes are not recognized names. However, in the scientific part of the application one can define the code and use it instead of the long winded scientific name.

If the product is not a new compound, it is recommended to research if an INN or proposed INN (pINN) already exists.

Medical Plausibility

The section A3 should comprise all information why it is expected that the medicinal product is or might be active in the treatment of the orphan condition. This should also include theoretical considerations describing the hypothesis between the development package. This is irrespective of the question whether there are non-clinical or clinical data available.

A draft guideline (currently under review) is available on elements to support the medical plausibility for an orphan designation.[38] That should be consulted when drafting these sections.

Relevant data to support the plausibility might include:

- Theoretical considerations
- In vitro/ex vivo studies
- Animal disease models
- Clinical data: studies including patients suffering from the orphan condition or case reports
- Clinical data from patients with related conditions
- Overview of important clinical or non-clinical safety data

Normally, data from an animal disease model are expected to reasonably support the medical plausibility. In fact, such models can be regarded as pivotal information in orphan designation requests for early stage projects[39]. In case a project is in development for a haematological cancer it is our experience that that successful applications without animal model are feasible. In such case studies providing data from ex vivo blood preparations from patients should be included. The argumentation that rodent xenograft models for haematological cancer do not reflect the disease adequately is recognized by the COMP. In any case, the relevance of the models should be discussed or clearly demonstrated.

Clinical data are also strongly support the assumption of medical plausibility. In case the activity of the drug has reasonably been demonstrated in the treatment of the orphan condition this does not necessarily raise major questions. However, if the data are inconclusive – as frequently seen in small phase IIa trials on orphan diseases – the discussion on significant benefit might be provoked. Similarly, in the case of phase I/II trials in oncologic

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[37] International Non-proprietary Name. For details see http://www.who.int/medicines/services/inn/en/

[38] "Guideline on Elements Required to Support the Medical Plausibility and the Assumption of Significant Benefit for an Orphan Designation (Draft)", EMEA/COMP/66972/2004, September 2004.

[39] "*Better to have a weak or early stage disease model rather than no disease model*", Dr. Rembert Elbers, German COMP member, July 2008, personal communication.

indications, frequently no response is seen. It is of course recognized that these trials do not aim at efficacy endpoints. Still it is the experience that lack of any efficacy raises the suspect of insufficient potency at the EMEA/COMP. It is therefore our experience that the designation process is smoother in such projects where only data from relevant disease models are available rather than early stage clinical data.

An important point on the adequate interpretation of any feedback of insufficient medical plausibility is that it can be regarded being a legal loophole that the request of medical plausibility is not included into the orphan regulation. The orphan regulation states that for the purpose of designation the product has to be intended (!) for the treatment of orphan conditions and that it has to provide significant benefit. The regulation does no explicitly state that its activity in the treatment of the orphan conditions has to be justified or demonstrated. For this reason, lack of medical plausibility is not an argument to justify a negative opinion. On the other hand, for obvious reasons the medical plausibility is of great importance for the designation process: designation for a product that is not plausible to offer any efficacy for the treatment of an orphan condition is not in the spirit of the orphan regulation. For this reason the COMP frequently uses an auxiliary construction to cope with such problems: if the concept behind the designation process is not plausible in a medical sense, no proper analysis and discussion of a potential benefit and therefore of the risk/benefit is possible. As a consequence, the significant benefit cannot be justified sufficiently. For this reason feedback on sections A3 (medical plausibility) and D3 (Justification of significant benefit) always indicate that there is some doubts with regards to the medical plausibility. In such cases particular focus should be set on the argumentation why the sponsor is of the opinion that the drug might be active in the treatment of the orphan condition.

Prevalence Estimation

The prevalence criterion is of outstanding importance for the definition of an orphan drug in the EU, i.e. the disease should not affect more than 5 per 10,000 individuals in the general population. In contrast to the American orphan definition, the threshold is defined as a fraction in the EU. This is reasonable as it accounts for changes in the population. The relevance of this approach is in particular obvious from the EU enlargement. The population comprised roughly 400 million people when the orphan regulation came into effect which corresponds to 200,000 patients in the EU. Today, the there are nearly 500 million inhabitants corresponding to a 25% increase to up to a quarter of a million orphan patients. If the orphan threshold had been defined initially on the number of patients (e.g. 200,000), due to the enlargement the prevalence would have decreased (4 per 10,000). In other words the diseases have to be rarer compared to the initial situation at end of last century. In fact, due to population increase such effects are obvious in the USA where the orphan criterion is defined as 200,000 cases (Orphan Drug Act, 1983)[40]. However, for unknown reasons in the public summary of opinions the COMP still states number of patients rather than the prevalence as a fraction.

The COMP has published *Points to Consider on the Calculation and Reporting of the Prevalence of a Condition for Orphan Designation* (26 March 2002)[41]. This document comprises several important information and proposals for drafting section B.

In general, it is important to note the difference between prevalence and incidence. Prevalence is defined as the number of persons with a disease or condition at a specific instant in time in a given population (sometimes called point prevalence). Incidence is the number of new cases during a defined period (typically one year). Under the assumption of stable

[40] It is tempting to speculate if it is chance that the prevalence of an orphan disease corresponded exactly to the number of patients that define the orphan threshold in the USA: 200,000.

[41] COMP/436/01

incidence and duration of the condition, the functional relationship between point prevalence, incidence and mean duration is commonly expressed as:

$$\text{Prevalence} = \text{Incidence} \times \text{Mean Disease Duration}$$

In addition, this function is only valid if the prevalence is small. However, as it is dealt with rare disease this requirement should always be met.

The duration should comprise the entire course of the condition. It is accepted by the COMP that mean or median survival is an adequate estimate for mean duration of the disease for most oncological indications as – generally spoken – cancer cannot be cured. This survival time should be derived from the data presented in section A.4 (Justification of the life-threatening or debilitating nature of the condition).

This approach appears to be of importance as for many diseases much more information on the incidence is available rather than prevalence. This is in particular true for oncologic conditions which comprise an important group or orphan conditions.

The most important sources for epidemiological information are:

1. Specialized Databases
2. Peer reviewed scientific literature

In the event that databases are available these are in most cases an important source of prevalence or incidence data. However, there is no general comprehensive database with public access that provides epidemiological information. Some commercial providers offer such packages of different quality. These are typically highly expensive and the use is not recommended for companies aiming only at single orphan designations. An important database with free access for information on oncologic conditions is GLOBOCAN[42]. In addition, for various diseases there are also national or supernational registries (e.g. information on solid organ transplant can be derived from Eurotransplant – an association of countries who share a common list of organ transplants). One of the comprehensive national registries is the UK National Health Service Statitics (see www.statistics.gov.uk).

Another source of data are hospital discharge registries. In such databases diseases are typically coded using ICD-9 or ICD-10. Table 9 comprises information on examples of such registries from European countries. The included examples Germany, Italy, France and England comprise approximately half of the EU population.

Table 9: Hospital discharge registries of some European countries.

Country	Registry	Access
England	Hospital episode statistics	www.hesonline.nhs.uk
France	Répartition des diagnostics principaux. Agence Technique de l`Information sur l`hospitalisation	http://stats.atih.sante.fr/mco/diagone.php
Germany	Gesundeitswesen, Diagnosedaten der Krankenhauspatienten. Statistisches Bundesamt Wiesbaden	www.destatis.de
Italy	Ricoveri, diagnosi ed interventi effettuati e durata delle degenze in tutti gli ospedali of the Ministero della Salute	www.ministerosalute.it

Another website containing important information on rare diseases is www.eurordis.org, the European Organisation for Rare Diseases. This includes also links to national organisations of rare diseases and other related topics.

[42] http://www-dep.iarc.fr/globocan/database.htm

There are two important sources of information that are not recognized by the EMEA. The first is “orphanet” (www.orpha.net), an internet portal for information on rare diseases and orphan drugs. However, it still provides important information on the orphan condition and in many cases on the prevalence as well. Such information should be listed but the application should not be based only on this database.

The second of these sources are the PSO published on the EMEA website following a finalized orphan designation process. These comprise information on the prevalence as estimated in the respective application. In case the orphan condition of interest is already recognized by the COMP, it is strongly recommended to compare the own results of prevalence estimation with the published information. This is an important opportunity to validate the results from this section.

In many cases peer reviewed scientific literature is the most important source for epidemiological information. Relevant papers can be identified on the basis of a research using databases such as Medline, Embase, SciSearch or similar (in fact, if possible as much databases as possible should be included as it is a frequent result that the same keywords yield at least in part different hits[43]). Of course, references in the identified literature should be hand searched for additional sources of data.

Particular focus should be set on data from the European Union[44]. In case, prevalence information from non-European (or even non-EU) countries are required to support the prevalence it should be clearly justified why these data are of relevance or representative for the EU population.

In case the identified data vary significantly, the sponsor should think about summarizing the information.[45] If the data source contains information on the cases observed and the underlying population, it is possible to summarize the information be means of calculating a weighted mean or performing a meta-analysis.[46] However, in some cases such analysis is not possible. Then the data should be summarized by stating the range. Such range might also be limited by rejecting the most extreme values. A similar approach is to include an analysis of the mode, i.e. the value that appears most frequently. Depending on the data one could also include a scenario analysis. For instance if one can state that the orphan criteria are fulfilled even in case conservative assumptions are made this will most likely be recognized. However, any approach like that should be justified and thoroughly discussed.

The prevalence should refer to the overall prevalence in the European Union. This implies that it is acceptable if higher values in single countries are observed as long as the total prevalence is below the orphan threshold. One example for such cases is tuberculosis, a

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[43] For example DIMDI offers the possibility to search these databases simultaneously: http://www.dimdi.de/static/de/db/index.htm

[44] It has turned out an successful approach to search the combination of the disease name, „incidence“ or „prevalence“ as keywords together with the names of all EU countries. This may sound laborious but frequently yields important additional information.

[45] A simple procedure to determine the precision of an estimated prevalence: Since prevalence is a proportion, a confidence interval can be obtained using the binominal distribution or, where there are at least five cases, the normal approximation to the binominal distribution. The variance of a point binominal random variable is pq (where p is the probability of a “success” and q=1-p), so that the standard error for the estimated probability is $\sqrt{(pq/n)}$. Thus the 95% confidence interval for a prevalence estimate p is: $p \pm 1.96\sqrt{[p(1-p)/n]}$. When there are fewer than five cases, an exact procedure is required.

[46] In a typical meta-analysis all cases of the studies included should be summed up and the figures of all underlying populations. The ratio of both sums is calculated in a second step. By this means all kind of information can be summarized that refer to fractions of populations, e.g. cases of mortality as a fraction of all patients or prevalence, i.e. cases of a disease as a fraction of the total population observed. The advantage to calculating the mean is that larger studies have a more pronounced impact on the total result.

recognized orphan disease in the Europe Union. The overall prevalence is approximately 2 per 10,000 but in eastern European countries the infection is more frequent with figures as high as 15 per 10,000 in Romania.

It should not be expected that epidemiologic data can be presented for all European countries this is only exceptionally the case. For this reason it should be argued why the data are representative for the whole European Community. This could for instance be achieved by demonstrating that information is provided from countries in Scandinavia, Central and Eastern Europe as well as from the Mediterranean countries as the major European regions with regards to climate and local culture. If there is only information from few countries one could also argue that the epidemiological data from several distinct European countries are similar and that for this reason the data are being regarded representative. One could also review how much of the European population is covered by the available data. Of course all reasoning can only be pursued if the data are appropriate. In any case it is strongly recommended to include such justification.

Formally, the application should include a sentence that the estimated prevalence is below the orphan threshold of 5 per 10,000 in the general population.

Authorized Treatments for the Orphan Condition

Section D1 should comprise an overview of all existing diagnosis, prevention or treatment methods. This includes pharmacological treatments as well as other therapies such as surgical interventions, physical means, diet, radiological techniques, etc. The pharmacotherapy options – i.e. drug therapy - should be clearly distinguished if they are authorized or off-label used. Only in case an authorized drug treatment for the condition exists section D.3 is applicable (see next section).

The authorized pharmacological treatment options for a particular orphan condition are not trivial to investigate. No public database exists where is summarized if a drug is authorized for the treatment of a particular orphan condition.

A successful approach is to identify in the first step which active substances are used. Such information can easily be derived from published reviews, treatment recommendations by experts or associations, etc. This results in a list of drugs that are used for treatment of the orphan condition. It has to be identified in a second step if these compounds are authorized or off-label used. Several national and European registries are available which can be hand searched on information concerning the legal status of the product of interest. It is strongly recommended to review as much national databases as possible if a medicinal product is not authorized on a European level. There are several examples for drugs with differing indications in the various countries. For instance cyclosporine is authorized for the treatment of autoimmune uveitis, a recognized orphan condition, in Germany, Ireland and Denmark but not in England and Sweden.

Medicinal products authorized under the centralized procedure are listed on the EMEA homepage (http://www.emea.europa.eu/htms/human/epar/eparintro.htm). Unfortunately, there is no search form for these data. In addition, the overview comprises only the brand name and the INN and not the condition or therapeutic indication. Information on the authorisation status of such centrally authorized drugs can also be derived from the European Commission Community register of medicinal products (http://ec.europa.eu/enterprise/pharmaceuticals/register/index.htm). The latter provides only a general overview of the products and procedures whereas detailed scientific information is also included into the EPARs (European Public Assessment Reports) which can be found in the former database. A search form for this data is available on the EudraPharm website (http://eudrapharm.eu/eudrapharm/searchbykeyword.do).

In addition, several national authorities offer databases on medicinal products in authorized in the respective country. A drawback is that such information is frequently available only in the local language. Table 10 presents some examples for such national registries.

Current experiences show that the COMP does not expect that the authorisation status for all European countries has to be reviewed. A representative overview of the most important countries is normally accepted.

Table 10: Examples for national registries of authorized medicinal products

Country	Source	Comment
Denmark	http://www.produktresume.dk/docushare/dsweb/View/Collection-96	Danish only
Germany	AMIS database on www.dimdi.de	DIMDI is an official organisation for information regarding the health sector
	www.fachinfo.de	Initial registration required
Ireland	http://www.medicines.ie/	-
Netherlands	http://www.cbg-meb.nl/CBG/en/human-medicines/geneesmiddeleninformatiebank/default.htm	-
Portugal	http://www.infarmed.pt/infomed/login.php	Portuguese only
Sweden	http://www.lakemedelsverket.se/Tpl/ProduktSearchPage____392.aspx	Swedish only
United Kingdom	http://emc.medicines.org.uk/	-

In addition, information on drugs authorized via mutual recognition or decentralized procedures can be obtained from the MRI product index on the Heads of Agency website (http://www.hma.eu/mri.html). This index contains information on authorisation date (date of day 90), MR number, authorisation holder, RMS and CMS as well as authorisation type.

Using a these sources usually allows the identification of sufficient data requested by the COMP. An adequate way of presenting such information is a summary table containing for each project at least information on:

- Active ingredient
- Trade name(s)
- Authorisation holder
- Member states where the medicinal product is authorized
- Authorized indication

In case the authorized product is generically available, it is accepted by the COMP that not all authorized drugs will be included into the table. Several representative examples can be presented and it should be stated that not all drugs are presented for reason of brevity and clarity.

Significant Benefit versus Satisfactory Methods

Depending if there is an authorized treatment for the orphan condition or not, only section D2 or D3 is applicable (but never both). It appears that errors during the application of

designation are most frequently related to this section which might also be due to the fact that the section headings are misleading. D2: *Justification as to why methods are not satisfactory* and D3: *Justification of significant benefit*. The request that currently available treatment methods are not satisfactory is a *conditio sine qua non* for granting orphan designation.[47]

In the event no treatment is authorized, one has to discuss why the current methods are not satisfactory. Current methods might include surgery, diet, physical therapy or even off label use of medicinal products. Whereas in section A.3 it is outlined in detail why a product is expected to be active in the orphan indication, it should be outlined in this section why there is a pronounced need. This request is based on the fact that the definition of an orphan condition in the EU comprises that is cannot be treated adequately. This is in most cases not too difficult. For instance one could summarize that despite all treatment efforts the mortality or disability is high (as summarized in section A.4).

In most cases there is already an authorized treatment available. In such cases, section D.3 is applicable. The sponsor has to demonstrate that a significant benefit compared to the currently available treatments can be expected. The logic of this approach is that for an authorized treatment a favourable risk/benefit has already been demonstrated which is interpreted in the way that they are therefore satisfactory. Of course this is not easy to understand. A drug treatment that improves the five-year survival rate of a malignancy from 10% to 20% with an acceptable safety profile will definitely have a favourable risk/benefit ratio and will also be of benefit for the patiens. But with four out of five patients dying, the situation is far from being satisfactory.[48] However, in the orphan designation process one has to cope with this interpretation.

In section D.3., it is recommended to include initially an outline that the condition cannot be treated adequately. As outlined, by means of referencing the data presented in section A.4 (Justification of the life-threatening or debilitating nature of the condition) it is usually no problem to demonstrate sufficiently that the condition cannot be treated adequately, despite the fact that there are authorized medicinal products available.

The above mentioned draft guideline also deals with aspects to support the assumption of medical plausibility.[49]

In general, significant benefit is defined in regulation (EC) No 847/2000 as a "*clinically relevant advantage or a major contribution to patient care*" (Article 3, (2)). Such advantage could be greater efficacy, an improved safety profile, improved pharmacokinetic properties, compliance promoting features, or evidences to show fewer interactions with food or medicinal products.

According to Article 3, (3), d), 3. "*major contribution to patient care*" is restricted to exceptional cases when neither greater safety nor greater efficacy has been shown. This could be applicable for cases where only one other medicinal product is authorized on a national basis not in all member states as in the example of autoimmune uveitis. One could argue that the OMP – which will be authorized under the centralized procedure – will be available to all patients whereas the availability of the currently available drug is restricted.

Such information should refer to features that result in a real benefit for the patient rather than to solving only theoretical problems. For example if a recombinant plasma protein shall be used instead of preparations from human blood benefits such as lower risk for infection with viral impurities require demonstrating that such infections are an issue in real life.

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[47] Regulation (EC) 141/2000, Article 3, 1. (b)

[48] In such case one might be able to argue that the new product has the potential to improve the patient survival.

[49] "Guideline on Elements Required to Support the Medical Plausibility and the Assumption of Significant Benefit for an Orphan Designation (Draft)", EMEA/COMP/66972/2004, September 2004.

For evident reasons the justification should be plausible and if possible based on experimental data (e.g. improved efficacy in a rodent disease model). Of course in early projects with only scarce data it is difficult to present real evidence for a significant benefit. Such analysis can also be performed on a theoretical basis. The list below will include some argumentation that has successfully been used in drafting orphan applications (which apply only in case corresponding data or information is available):

- New mode of action offers the possibility of benefit for those patients not responding appropriately to authorized treatments (in such cases a sound medical plausibility is of particular importance).[50]
- Possibility of combination therapy using the new treatment and available therapeutic options to improve the overall efficacy

However, in any case a reasoning based on experimental data should be used preferably rather than pure theoretical considerations.

It is recommended to outline a consistent argumentation in the application. In the ideal case in section A4 (Justification of the life-threatening or debilitating nature of the condition) it is presented which features of the condition justify the assumption that it is a severe disease. It should be presented if possible that such issues might be improved by means of the new product.

In fact, questions concerning the justification of significant benefit are one of the most frequently observed issues during validation by the EMEA and evaluation by the COMP. However, it should be noted that the COMP might also raise the question for significant benefit in case the medical plausibility has not sufficiently been demonstrated as discussed in more detail. For this reason this section should be drafted with particular care.

Overall Strategy

The applicant should try to provide a comprehensive picture of the program. The interrelation between the different sections should become obvious. Frequently the medical plausibility (section A.3) is justified on the pathophysiology of the disease (A.1). In section A.4 it is presented why the disease can be regarded being severe and/or serious. The applicant should include into the argumentation the effects of available therapies (as summarized in D.1) to cope with features such as high mortality or severe disablement. In most cases the data presented in section A.4 refer to patient treated according to state of the art – this helps to justify the medical need (required for sections D.2/3). A justification of significant benefit should be based on the known features and effects of the drug as summarized in the medical plausibility (A.3). In addition, in the ideal case section D.3 (Justification of beneft) should convince that the new product might relieve severe factors as presented in section A.4. Similarly, in case in the prevalence section (B.1) the prevalence is calculated on the basis of the disease duration or survival time and incidence the former figures should also be justified on the basis of information from section A.4.

Prevention or Diagnosis of an Orphan Condition

In case the orphan medicinal product is intended for diagnosis or prevention of a disease it has to be noted that the prevalence estimation should not only refer to the real cases rather than to the population that could be theoretically affected. For instance if a new diagnostic method for glioma is presented or a vaccine for avian flu the epidemiological information should not refer to observed cases of glioma or infection with influenza H5N1 rather than the population that could be affected by this condition (and could be for this

[50] It should be discussed why the new mode of action could translate into an improved efficacy. In the ideal case a direct comparison to the authorized drug has been made in the relevant disease models.

reason receive a vaccination or undergo diagnosis for the malignancy). Evidently this request increases in most cases the target population significantly (in fact for the two conditions mentioned it will be more or less the whole European population). It is most likely due to this fact that only a minority of orphan designations refers to prevention or diagnosis. From an epidemiological point of view it should be no problem if a product is intended to diagnose or prevent complications of an orphan condition (e.g. prevention of rejection episodes after organ transplantation falls into this class). Similarly, the diagnosis of the extent of an orphan condition (in cases with proven diagnosis) should also be feasible (one example is diagnosis of the extent of histologically proven amyloidosis, EU/3/03/134).

Questionnaire on the Orphan Designation Process

To identify the most critical sections of an orphan medicinal product designation request a survey was carried out. A questionnaire was sent by email to all sponsors of orphan medicinal product designations of the last three years. Confidentiality was confirmed to the sponsors and the document was designed in such a way that it did not allow any direct conclusion to the project. For this reason information on the disease area were not included although it is expected that this would result in instructive information. All returned questionnaires were analysed in a purely statistical fashion.

This questionnaire used is attached in Annex I.

Results

A total of 103 companies were contacted in July 2008. Twelve contact email addresses as listed in the PSO resulted in error messages resulting in 91 successful enquiries. A total of 28 (31%) answers were obtained till August 2008.

Below some particular aspects are presented and discussed in more detail. In all cases where the sum of presented studies is less than 28 this is due to the fact that no answer was given for part of the questions ("unknown/confidential"). Proper analysis of the available data is impaired by the fact that the total number of projects is relatively low. Still, for most questions the significance can be reasonably assessed.[51]

It was initially analyzed if there are factors that have a positive influence on the validation process. Overall in only 26% (7/27) of all applications no validation issues were raised at all. This means that three out of four applications had to be resubmitted. However, according to this survey an initial pre-submission meeting increases the probability that no issues will be raised during validation threefold: In only 29% (2/7) of those applications where a pre-submission meeting took place had some queries compared to 86% (18/21) of the projects without prior discussion with the EMEA. Despite the small number this difference is significant (Fischer's exact test: $P = 0.009$). In both cases where validation issues were raised despite prior discussion with the EMEA, these issues referred in particular rather than the content of the scientific part of the application. No other factor was identified that influenced the probability of quick and smooth validation (such as authorisation status of the product in other indications, availability of clinical data, or if the condition was recognized being orphan). The sections that were most often criticized during validation were A.3 (Medical Plausibility) in 42% (8/19) of the cases and D.3 (Justification of significant benefit) in 37% (7/19) of the cases. In our experience wrong classification of a product (i.e. D.2 or D.3 or the question if there is an authorized treatment or not) is one frequent issues raised during validation. According to this survey in approximately every second case (10/19) where issues were identified by the EMEA these included the section D in general.

[51] For use of the Chi square test or the Fischer's exact test see S.A. Glantz "Primer of Biostatistics", Sixth Edition, 2005, Chapter 5.

As mentioned earlier, the initial review by the EMEA prior to the formal COMP review procedure also comprises issues with regards to content to support the COMP. Data from the analysis of this questionnaire allow estimating the impact of such pre-review performed by the EMEA. For total of 40% (8/20) of all projects where the EMEA raised validation issues a list of question was obtained from the COMP. In contrast the COMP issued in 50% (4/8) of all cases a list of questions where no potential problems were identified during the EMEA validation. The ratio between both percentages is 1.25 and not significant (Fischer's exact test: P = 0.290). Due to the small number a clear estimation on the relevance of the checking for content cannot be performed but the available data do not support the assumption that this pre-review has any benefit for the overall assessment.

In total the COMP issued a list of questions in 43% of all cases included (12/28). Again sections A.3 (Medical Plausibility) and D.3 (Justification of significant benefit) are most frequently questioned by the COMP (42% [5/12] and 58% [7/12] of all cases where questions were raised).

Only two of 28 projects referred to medicinal products that were already authorized at the time of submission. The data indicate that the authorisation status of the product in other indications has no influence if issues might arise during the designation process as 50% (1/2) of authorized drugs received a list of questions from the COMP compared to 42% (11/26) for the new drugs with the difference being not significant (Fischer's exact test: P = 0.508).

In every second project the condition was already recognized as an orphan disease at the time of designation (14/28 corresponding to 50%). Subanalysis revealed that the procedure for drugs against recognized orphan diseases received in approximately half of the cases questions compared to diseases that are presented the first time to the COMP (29% [4/14] versus 57% [8/14]). Most likely due to the small number of cases the difference is not significant (Fischer's exact test, P = 0.099). Interestingly, in three of the four cases where some questions had to be discussed with the COMP the issues referred to section D.3, the justification of significant benefit.

A total of 71% (20/28) of all applications comprised some kind of clinical data for the investigational product. These data were in 65% of all cases (13/20, or 46% of all applications included) phase II or phase III data on the orphan condition or at least case reports, i.e. clinical information on the use of the product in treating the orphan condition. Neither the existence of clinical data nor the existence of clinical data in the orphan condition has any influence if a list of questions was issues (clinical data versus no clinical data 33% [4/12] versus 50% [8/16] received LoQ; clinical data from the orphan condition 50% [7/14] versus 43% [6/14]; both differences being not significant, Fischer exact test P = 0.209 and P = 0.275).

It was stated above that it might happen that sponsors travel to the EMEA for responding the questions issued by the COMP and is informed that no hearing is required as the issues were resolved on the basis of the written response. This appears to happen as often as in 20% (2/10) of all cases when the sponsor is invited for a hearing (95% confidence interval (CI): [6%; 34%]).

In a previous section proper definition of the orphan condition was discussed in great detail. A total of 19% (5/26) of all respondents reported that there have been particular discussions with regards to the definition of the orphan condition during the designation procedure. However as already mentioned in every second application the condition was already recognized at the time of designation making particular issues with regard to the definition unlikely. In fact in all four cases where such discussions occurred the orphan condition was not recognized at that time being orphan. Accordingly for "de novo application on a new condition" in 36% of all cases the definition of the orphan condition was challenged by the EMEA/COMP (95% CI: [20%; 52%]). This strongly supports the recommendation to carefully and thoroughly analyse if the condition fulfils the criteria being set.

Conclusion and Summary

Issues are frequently raised during validation of orphan designation requests. The probability of a smooth procedure at the EMEA can be significantly increased if a pre-submission meeting is held initially. Most frequently validation issues refer to the medical plausibility or the justification of significant benefit.

No clear risk factors could be identified for receiving a list of questions. Neither the authorisation status of the medicinal product at the time of designation, nor the existence of clinical data had any impact raising a list of questions by the COMP. A non significant trend was observed for question if the condition was recognized being orphan at the time of designation. Applicants on recognized diseases tend to be reviewed with less discussion. The most important issue raised by the COMP is the question is significant benefit is adequately justified.

The data support the importance of proper defining the orphan condition as this is the reason for debate in more than every third application where it is applied the first time for the respective orphan condition.

Negative Opinions

The EMEA contains only very few negative opinions in their register of Public Summary Opinions on orphan designation[52]. This is most likely due to the fact that during the Day 90 hearing the applicant gets typically the opportunity to withdraw the application if it becomes apparent that the COMP will not support the designation.

Strategy to Avoid Public Information on Negative Opinions

It is recommended to the applicant to withdraw the application as soon as it becomes obvious during the COMP hearing that a negative opinion will be adopted. As outlined this is typically offered to the sponsor during the process. The application can be resubmitted again after the issues raised by the COMP have been addressed appropriately. In case the issues raised can not be invalidated by new data (e.g. if the condition is not accepted) such withdrawal has the advantage that no information on the negative evaluation of the COMP will become public which is typically not favoured by the applicant.

Against this background it can be questioned why the sponsors of the products resulting in a negative opinion did not take such advantage. One consequence of a negative opinion is that a Public Summary or Opinion is presented on this project stating the reasons for the evaluation of the COMP.

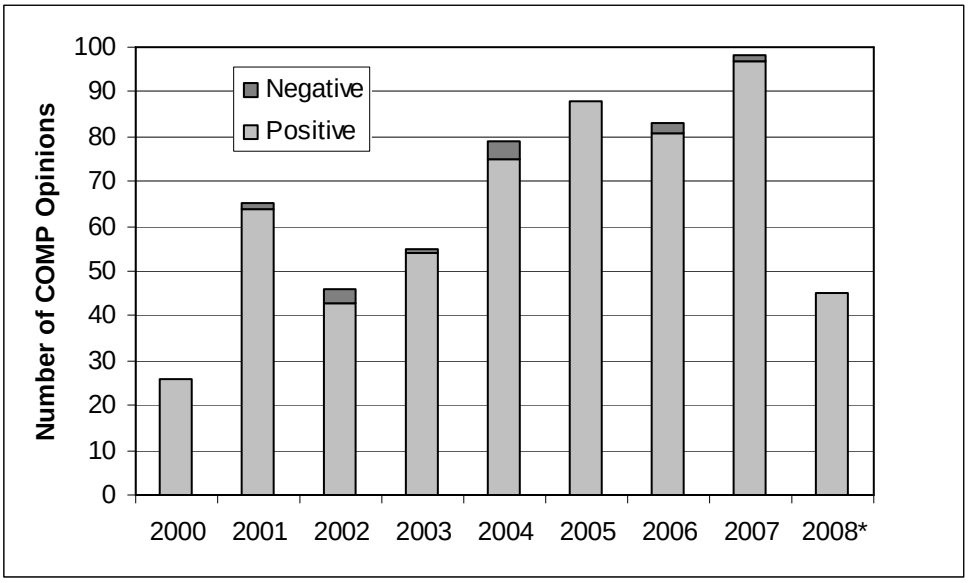
Public Information on Negative Opinions

In total since the orphan medicinal product regulation came into effect in 2000 a total of 585 applications have been submitted to the EMEA[53]. Only twelve applications received a negative opinion (corresponding to 2%). These figures are illustrated in Figure 1.

[52] http://www.emea.europa.eu/htms/human/orphans/opinions.htm

[53] As off August 2008

Figure 1: Overview of the number of positive and negative opinions for orphan designation requests.



* January till July 2008

From this figure it becomes in particular obvious that only in exceptional cases a negative opinion by the COMP. However, it should be noted that there is no information with regards to applications withdrawn during the procedure. Table 11 contains detailed information for ten of these twelve orphan medicinal product applications with negative outcome.

Table 11: Overview of products with a final negative opinion by the COMP.

Medicinal Product	**Condition**	**Date**	**Reason for Opinion**
Capsaicin	Treatment of painful HIV-associated neuropathy	April 2006	1. Condition not regarded as valid subset 2. No data to establish that peripheral neuropathy affect not more than 5 in 10,000 people in the Community 3. No sufficient justification for significant benefit
Chelidonii radix special liquid extract	Treatment of pancreatic cancer	December 2007	No sufficient justification for significant benefit
Chlorproguanil hydrochloride and dapsone	Treatment of acute uncomplicated *Plasmodium falciparum* malaria	May 2002	No sufficient justification for significant benefit

Histamine dihydrochloride	Treatment of malignant melanoma	January 2004	1. Condition not regarded as valid subset 2. No data to establish that malignant melanoma affect not more than 5 in 10,000 people in the Community
Ibritomomab tiuxetan for use with ^{90}Yttrium[54]	B-cell non-Hodgkin´s lymphoma	March 2001	1. Condition not regarded as valid subset 2. No data to establish that B-cell Non-Hodgkin's lymphoma affect not more than 5 in 10,000 people in the Community
Ibuprofen L-lysinat[55]	Treatment of patent ductus arteriosus in premature neonates of less than 34 weeks of gestational age[56]	September 2004	1. No data to establish that patent ductus arteriosus in premature neonates of less than 34 weeks of gestational age affects not more than 5 in 10,000 people in the Community 2. No sufficient justification for significant benefit
Midazolam hydrochloride (for oromucosal use)	Treatment of seizures which continue for at least five minutes	July 2003	No data to establish that patent seizures which continue for at least five minutes affect not more than 5 in 10,000 people in the Community
Mycobacterial cell wall complex	Treatment of superficial bladder cancer	September 2002	1. Condition not regarded as valid subset 2. No data to establish that superficial bladder cancer affects not more than 5 in 10,000 people in the Community
Sudismase	Treatment of active phase of Peyronie's disease	November 2004	1. Condition not regarded as valid subset 2. No data to establish that Peyronie's disease affects not more than 5 in 10,000 people in the Community
Tramadol hydrochloride	Treatment of painful HIV-associated neuropathy	April 2006	1. Condition not regarded as valid subset 2. No data to establish that peripheral neuropathy affect not more than 5 in 10,000 people in the Community 3. No sufficient justification for significant benefit

It should be noted that in those projects where the condition was not regarded as a valid subset additional reasons for rejection refer to the general condition rather than the subset. For instance if "active phase of Peyronie's disease" is not regarded as a valid subset the further analysis of the COMP refers to Peyronie's disease.

For nine different projects details on the reason for the negative opinion were obvious. In seven the reason for the negative opinion was based on the fact that the disease was not considered as a valid subset (i.e. in 78%). The problem with subsets has been discussed in detail above. The second important reason for the negative opinion was no sufficient justification for significant benefit highlighting once more the importance of this aspect.

[54] Since 2004 this product is authorized as Zevalin® for the treatment of B-cell nin-Hodgkin's lymphoma – but not as an orphan drug.

[55] Two negative opinions on this medicinal product in the condition are presented.

[56] Interestingly, Pedea (with ibuprofen as drug substance) is authorized as an orphan drug for the treatment of haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age since 2001. Most likely the sponsor of the unsuccessful application could not demonstrate sufficiently the benefit caused by the stereochemical pure lysinate salt which would also most likely fall under the similarity claim.

In conclusion this analysis clearly shows that proper definition of the condition is of great importance. A not accepted subset of a disease is the most frequent reason for the rejection of an orphan application.

DEVELOPMENT OF ORPHAN MEDICINAL PRODUCTS

The development of orphan medicinal products is characterized in particular by two peculiarities: First orphan diseases are rare and for this reason the recruitment of patients might be a challenge. Second, orphan conditions are severe diseases which makes a positive risk/benefit ratio easier to achieve.

Maintenance of an Orphan Designation

There are two levels of maintenance after the initial designation for orphan medicinal products under development. The first refers to annual reports that have to be submitted till the initial request for marketing authorisation is filed. The second level of maintenance refers to an early step in marketing authorisation: The sponsor is obliged to apply for reconfirmation by the COMP if the orphan criteria are still fulfilled for the respective project.

Annual Reports

The sponsor of an orphan medicinal product is obliged to provide annual reports on the state of the development[57]. This report has to be submitted with in two months after the European birth date, i.e. the date of the decision of the European Commission. In case there is uncertainty this date can be derived from Community register of OMP[58]. Interestingly it is not stated in the orphan regulation what happens if a sponsor does not submit the annual report.

Details on format and content are summarized in a particular guidance document[59]. In particular an updated version of the orphan form should be submitted. All modified sections should also be highlighted in the cover letter.

The annual report itself should be written in English and address the following issues covering all advances since initial designation or the last annual report.

- Development advances including an tabulated overview of ongoing initiated, ongoing or completed preclinical and clinical studies as well as a short summary of the studies.
- Update on regulatory status of the product in EU and non-EU countries (Compassionate-use programs, orphan designations, marketing authorisations)
- Summary on incentives received

Such report can be kept short with a few pages being in most cases sufficient. No study reports have to be included unless explicitly requested by the EMEA. One signed and dated original plus one copy as well as an electronic copy of the report in word-processable format should be submitted to the EMEA (Scientific Advice & Orphan Drug Sector).

Maintenance in Relation to Marketing Authorisation

When sponsors of an orphan-designated medicinal product submit a marketing authorisation application, they should submit in parallel a report on maintenance of the orphan crite-

[57] Regulation (EC) No 141/2000, Article 5, 10.

[58] http://ec.europa.eu/enterprise/pharmaceuticals/register/alforphreg.htm

[59] *Note for Guidance on the Format and Content of the Annual Report on the State of Development of an Orphan Medicinal Product*, 30 April 2002, COMP/189/01.

ria[60]. This report will be reviewed by the COMP between day 121 and 180 of the centralized procedure. The COMP will forward their statement on the maintenance of the orphan status to the CHMP.

For the purpose of the update of designation a template can be found on the EMEA website.[61] This report comprises information on a potential change of the prevalence or the life threatening/debilitating nature of the disease. In addition, the justification of significant benefit has to be updated (or of course the significant benefit). The latter is the orphan criterion where most change might have taken place since the time of initial designation.

However, current experiences indicate that generally the maintenance of the orphan status during the marketing authorisation process is no major problem.

Protocol Assistance

One of the advantages during the development of an orphan medicinal product is that it qualifies for total fee redemption for scientific advice – called "Protocol Assistance" in the context of orphan medicinal products.[62]

In fact, this is also highlighted by the fact that in the above mentioned questionnaire 80% of all respondents reported that they planned to seek scientific advice at the EMEA or did already. There was consensus that the advice was helpful (six positive answers and one "unknown/confidential" compared to no negative feedback). However the fraction cannot be determined as the total number of obtained advice is unknown.

It will be outlined in the section below that there is some evidence from the available data of authorized orphan medicinal products that the authorisation procedure was smoother for projects where PA was obtained (see below).

Although Protocol Assistance is regarded being an important support in successful development of orphan medicinal products an in depths analysis of this procedure is beyond the scope of this thesis.

Non-Clinical and CMC Development

The characteristics of orphan conditions in particular to clinical features such as rarity of patients, severity of the disease and lack of therapeutic options in the treatment. As will be outlined in the following sections this can have a significant impact on the development planning – in particular if compared to non-orphan medicinal products.

On the other hand, it is evident that the requirements from a non-clinical development and quality perspective are the same for orphan and non-orphan medicinal products. None of the difficulties described above should have any impact on this work. Accordingly, all regulatory guidance for the Modules 3 and 4 of the CTD are fully applicable in the development of orphan medicinal products. Still, some authors notice methodological limitations during the non-clinical development of OMPs (Joppi et al., 2006).

For this reason, the focus of this part on the development of orphan medicinal products will be on clinical development.

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[60] For this purpose the EMEA will contact the applicant.

[61] http://www.emea.europa.eu/htms/human/orphans/maintenance.htm

[62] Guidance on the overall procedure can be found at:
www.emea.europa.eu/htms/human/sciadvise/Scientific.htm

"Small Population Guideline"

The CHMP efficacy working party has prepared in joint collaboration with members of the Scientific Advice Working Party (SAWP), the Paediatric Expert Group (PEG) and the COMP a guideline considering problems associated with clinical trials when there are limited number of patients available to study which is for evident reasons a frequent problem in the development of orphan drugs: *Guideline on Clinical Trials in Small Populations* (26 July 2007)[63].

It is evident that all trials should be performed following the GCP principles, in particular as data of highest quality should be ensured.[64]

The general principle is that if feasible randomized controlled trials should be performed. Controlled studies with low statistical power should be preferred over uncontrolled trials. However, it is understood that due to the severe nature of the disease a placebo group which would be a preferred comparator cannot be employed due to ethical constraints. It might furthermore not be feasible to include an active comparator as no adequate treatment is available. In the event an active comparator with no good evidence is included it should be aimed at superiority over the comparator. In some cases within patients comparisons are feasible, i.e. comparison to baseline. Such procedure can be employed by relentlessly and predictable progressive disorders as for instance some metabolic disease requiring substitution therapy.[65] In case no adequate treatment control is available historical controls might be acceptable.

There are no special methods for designing, carrying out or analyzing clinical trials in small populations. Similarly, no methods exist that are relevant to small studies that are not also applicable to large studies. There are however approaches to increase the efficacy of clinical trials with greatest impact in situations where only few patients are available. The need for statistical efficiency should be weighted against the need for clinically relevant/interpretable results - the latter being most important.

Ideally a "hard" and clinically relevant endpoint should be chosen for efficacy analysis, such as survival or even cure of a disease. However, endpoints of intermediate levels, such as "time to disease progression" are also feasible. In some cases, the endpoint might refer to complications directly related to the orphan condition. These complications should directly impair the patients survival or well-being (e.g. renal failure in patients with Fabry's disease, a hereditary galactose deficiency). Despite the fact that quality of life is important for the patients it is unlikely that this will justify a marketing authorisation if no other benefit is obvious. Biomarker or surrogate endpoints are also feasible but these should be validated and discussed in the context of the overall disease and treatment effects.

During the trials, measures should be taken to minimize the "bio-noise" – the sum of non-systematic errors in a trial – as these usually leads to a bias towards failing difference between treatments. These include for instance loss to follow up which can be reduced by including ensuring visits scheduled at reasonable and convenient times for patients, providing transport etc.

In the design of studies it should be taken into consideration that continuous variables usually allow smaller sample sizes than categorisations into responder and non-

[63] CHMP/EWP/83561/2005, 27 July 2006

[64] This should be a common place but there are in fact examples that orphan products were not authorized due to poor data quality. See section *Negative Opinon*.

[65] It will be presented in Table 18 that this approach is frequently used in the development of orphan products.

responder.[66] Matching ore randomisation may also improve power, in particular if it is based on prognostic variables.

The guideline furthermore suggests three types of study designs that might be employed in the development of orphan medicinal products:

- Sequential design
- Response adaptive methods
- N-of-1 designs

These will be presented in some detail in the next sections.

Sequential Designs

Generally, sequential designs include a decision point during the trial if or how to continue the study. In group sequential designs the study results are analysed after treatment of single or only few patients before these patients continue the study or before further patients are randomized. The study will only be continued if predefined criteria are fulfilled. This principle can also be employed in long-term studies for the safety and efficacy of a new treatment if interim analyses are performed.

The predefined stopping boundaries with regards to safety or efficacy need not being symmetrical. In active comparator trials a stopping criterion for futility may also be introduced.

To improve the information value of the results after an interim analysis in blinded trials the sponsor should install an independent Data Monitoring Committee (DMC).[67] This board shall analyse the interim data and make a recommendation on the further procedure.

Preferably the data required for the decision if or how the trial is continued should be available quickly in relation to patient recruitment.

One of the main advantages of sequential designs is the general reduction of the required samples size. The disadvantage of this approach is that the study times are fairly long and the overall planning and performance is complex.

Adaptive designs as outlined below can be regarded as a special case of sequential designs in general.

Response Adaptive Methods

An adaptive design incorporates emerging information from the trial into the assignment probabilities in an attempt to assign more patients to the treatment performing better thus far in the trial (Rosenberger & Lachin, 1993; Rosenberg, 1999). Accordingly, such methods base the treatment assignment probabilities on the success of treatment with regard to the primary outcome of the trial. The more patients respond to the therapy the higher will be the fraction of future patients randomized to this treatment (for this reason they are sometimes called “the-winner-plays)”. This scheme increases the probability that a volunteer will receive the treatment performing better. Usually, this requires a dichotomous outcome for the patients, i.e. treatment success or failure. Continuous unblinding and analysis of individual data is a prerequisite for the conduct of such studies. The method is most suited in cases where only two treatments are compared. It gets much more complex if an additional third group is included into the trial.

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[66] However, it will be shown in Table 18 that in less than 40% of all authorized orphan products the primary endpoint will be a continuous variable.

[67] Please see also “*Guideline on Data Monitoring Committees*”, EMEA/CHMP/EWP/5872/03 Corr, 27 July 2005

It is obvious that these trials are only feasible in indications where outcome parameters are available quickly in relation to the patient recruitment. Theoretically one could use this method to investigate the influence of a particular treatment on the survival in cancer but the overall study would then be several decades. One can imagine the use of such principles for instance in the treatment of pain or in emergency therapy such as treatment of cardiogenic shock, a recognized orphan disease. No example could be identified where this method was investigated in the treatment of any orphan condition.

A disadvantage is that there is no procedure how to take secondary outcomes into consideration in the adaption process. This can be of importance for additional efficacy parameter as well for safety endpoints. Another problem is that the logistics in such trials can become very complex. A close collaboration between statisticians, clinicians and people responsible for trial supply must be ensured.

In a variation of this method, response adaptive designs are used for dose finding. As they tend to find the optimum dose quicker and they treat more patients at the optimum dose and estimate the dose more accurately such methods are encouraged. Such dose findings, together with seamless phase II/III trials and sample size re-estimations are the fields where it is supposed that adaptive designs can be used beneficially (Gallo et al., 2006).

N-of-1 Trials

This approach can be regarded as a cross-over study performed in single subjects. In contrast to traditional cross-over trials the primary purpose of the N-of-1 trial is to establish effects in an individual whereas cross-over trials establish effects on a group (Guyatt et al., 1988). The patient's first treatment is randomized, following treatments can be determined by randomisation or by a predefined switch. Ideally, this approach should be a controlled double-blind setting. One or multiple switches may occur. Treatment periods should be separated by an adequate wash-out periods to avoid any interference of the results due to carry-over effects. At the end the effects on the different dosing periods are analysed. Series of such single subjects may be performed and the results may be summarized in a statistical overall analysis (Wegman et al., 2006; Zucker et al., 1997).

The most important prerequisites are that the OMP is intended for the treatment of chronic stable conditions. The drug should have a rapid onset of action and rapid cessation of effect after discontinuation (see for instance Cook, 1996). Similar to other cross-over designs this approach is also not suited for the development of drugs expected to cure a disease (such as many antibiotics) rather than for symptomatic treatment.

Due to the severe and fatal character many of the recognized orphan diseases are not applicable for such a treatment approach. This is in particular true for most oncologic indications[68]. However, there are several examples where one might envisage such designs, such as treatment of particular forms of pain or sleep disturbances. Another example is the use of nebulised recombinant human desoxyribonuclease (DNase) in the treatment of cystic fibrosis[69]. As earlier trials demonstrated that individual responses are unpredictable a series of N-of-1 trials was performed with the aim to investigate how DNase can be targeted to those cystic fibrosis patients who would benefit most (Böllert et al., 1999).

[68] On the other hand complications of cancer treatment can be investigated using serial N-of-1 studies. For instance Sung and colleagues investigated the efficacy of vitamin E in the prophylaxis of oral mucositis caused by doxorubicin-containing chemotherapy in paediatric patients (2007).

[69] With 14 orphan medicinal product designations (excluding infections in CF) cystic fibrosis is one of the most prominent examples for orphan diseases.

Data Analysis

Overall it is strongly recommended to use elaborated statistical methods to analyse the data rather than only "simple" descriptive statistics. The guideline puts forward some methodologies that could be employed:

- Use of non-parametric methods if the distribution type of the data is not known (such as Normal distribution).
- The use of prognostic variables for stratification might greatly enhance the precision of a treatment effect.
- Repeated measurements over time may improve the efficiency of analysis.
- Bayesian methods – i.e. a methodology to compute posterior probabilities on given observations – might be advantageous in the interpretation of data from small populations.

Evidently a case by case decision has to be made and the approach chosen should be justified.

Relevance of the Guideline

Overall, the guidance cannot provide a general solution how to cope with few patients. However, it offers some tools and general principles to derive the maximum amount of information from studies.

The design principles listed in the guideline may in fact be of relevance for reducing the sample size required but most of them are applicable only to symptomatic therapy or to treatments where patient results are quickly available. This situation exists for some orphan diseases but is an exception rather than the rule.

As will be presented below some of the principles – such as use of comparator groups – were frequently not taken into consideration during the development of the currently authorized OMPs. In addition, to our information there is no authorized OMP where special designs such as the N-of-1 approach were used. However, this might in part be due to the fact that this guideline has been published approximately two years ago and that the clinical strategy for the currently authorized products was defined at a time prior to the availability of this guideline. Accordingly, the impact of this guideline has yet to be awaited.

Comparison of Orphan and Non-Orphan Medicinal Products

To gain some information of potential similarities or differences between orphan and non-orphan ("normal") medicinal products during development and authorisation, data on several characteristics and features of these drugs were compared. The source of information was in most cases the European Public Assessments Reports (EPAR) that are published on the EMEA website some time after marketing authorisation. However, for evident reasons there is only limited information available that can be used for such analysis.

In the following section, the strategy will be presented to compare both classes of drugs on the basis of selected OMPs and matched reference products (i.e. non-orphans). The further analysis will frequently use this data set as a basis but in most cases information derived from all orphan medicinal products will also be included.

Orphan Medicinal Products and Reference Compounds

In this analysis all orphan medicinal products were included that were not authorized with bibliographic data only (i.e. well established use authorisation). As far as possible comparator – i.e. authorized non-orphan drugs – were identified for orphan medicinal products on the basis of characteristics such as indication class (oncology, metabolic, cardiovascular (CV) or CNS etc) product type (protein versus small molecule) or approximate authori-

sation date. In few cases medicinal products were authorized for orphan conditions but not as orphan drugs (e.g. Velcade for the treatment of multiple myeloma). In such case comparison was done with OMPs for the same condition if feasible.

Following this approach in total 18 matched pairs of orphan medicinal products and non-orphans were identified. An overview on this products and the rationale is presented in the table below. Details on the orphan medicinal products and reference products can be derived from Annexes II and III.

Table 12: Comparison of selected orphan drugs and assigned reference products

OMP	**Reference**	**Justification for Matching**	
Cystadane	Adenuric	Active ingredient	Betaine/febuxostat (small molecule)
		Therapeutic field	Metabolic
		Mode of action	Lowering levels of deleterious metabolites
		Authorisation	2007/2008
Diacomit	Vimpat	Active ingredient	Stiripentol/lacosamide
		Therapeutic field	CNS (Stiripentol)
		Authorisation	2007/2008
Inovelon	Zonegran	Active ingredient	Rufinamide/zonisamide (small molecule)
		Therapeutic field	CNS (anti-epileptics)
		Mode of action	Modulation of sodium channels
		Authorisation	2007/2005
Litak	Zevalin	Active ingredient	Cladribine/ibritumomab tiuxetan
		Therapeutic field	Oncology (lymphoma)
		Authorisation	2004/2004
Nexavar	Tyverb[70]	Active ingredient	Sorafenib/lapatinib (small molecule)
		Therapeutic field	Oncology
		Mode of action	Tyrosine kinase inhibition
		Authorisation	2006/2008
Prialt	Lyrica	Active ingredient	Ziconotide/pregabalin (small molecule)
		Therapeutic field	CNS (pain)
		Mode of action	Neuronal calcium uptake modulation
		Authorisation	2005/2004
Revlimid	Velcade	Active Ingredient	Lenalidomide/Bortezomib (small molecule)
		Therapeutic field	Oncology (multiple myeloma)
		Mode of action	Unknown/proteasome inhibition
		Authorisation	2007/2004
Savene	Cyanokit	Active ingredient	Dexrazoxane/hydoxocobalamin (small molecules)
		Mode of action	Antidotes for acute intoxications
		Authorisation	2006/2007
Soliris	Extavia	Active ingredient	Eculizumab/Interferon beta 1b (protein)
		Therapeutic field	Autoimmune disease
		Authorisation	2007/2008

[70] August 2008: Conditional approval

Somavert	Aclasta	Active Ingredient	Pregvisomant/zoledronic adid*
		Therapeutic field	Mucosceletal (erratic growths[71])
		Authorisation	2002/2004
Sutent	Tarceva	Active Ingredient	Sunitinib/erlotinib (small molecule)
		Therapeutic field	Oncology (solid tumor)
		Mode of action	Tyrosine kinase inhibition
		Authorisation	2005/2006
Thelin	Exforge	Active Ingredient	Sitaxentan/amlodipine + valsartan (small molecules)
		Therapeutic field	CV (hypertension)
		Authorisation	2006/2007
Tracleer	Kinzalkomb	Active Ingredient	Bosentan/telmisartan + hydrochlorothiazide (small molecules)
		Therapeutic field	CV (hypertension)
		Authorisation	2002/2002
Trisenox	MapCampath	Therapeutic field	Oncology (haematologic)
		Authorisation	2001/2002 (exceptional circumstances)
Volibirs	Rasilez	Active Ingredient	Ambrisentan/aliskiren
		Therapeutic field	CV (hypertension)
		Authorisation	2008/2007
Xyrem	Circadin	Active ingredient	Sodium oxybate/melatonin (small molecules)
		Therapeutic field	CNS (sleep disturbances)
		Authorisation	2005/2007
Yondelis	Temodal	Active Ingredient	Trabectedin/temozolomide (small molecules)
		Therapeutic field	Oncology (solid tumor)
		Mode of action	DNA modification
		Authorisation	2007/1997
Zavesca	Galvus	Active ingredient	Miglustat/vidagliptin (small molecules)
		Therapeutic field	Metabolic
		Authorisation	2002/2007

* small molecule and protein

In the following sections these drugs will be compared to collect information with regards to differences in the development and authorisation of orphan medicinal products compared to non-orphan drugs.

The properties compared between orphan and non-orphan medicinal products are:

- Number of patients during development
- Number of main studies submitted for initial marketing authorisation
- Significance of results with regards to the primary endpoint
- Choice of comparator group

[71] Acromegaly and Paget's disease

- Frequency of pre-authorisation inspections
- Number of list of questions obtained during the authorisation process
- Time to answer of the first list of questions

The former three features will be analysed in this section, the latter in the section "*Authorisation of Orphan Medicinal Products*".

Prior to analysis the question was pursued if the selected 18 OMPs are really representative of all authorized orphan drugs. The table below summarizes the comparison between the selection and the population of all orphan medicinal products with regards to some of the parameter analysed.

Table 13: Comparison between selection of OMPs and all authorized OMPs

Parameter	All Orphan Drugs	Selection	Significance
Number of main studies*	1.84±1.20	1.84±1.14	P = 0.43
Fraction of studies without comparator group	30%	29%	P = 0.25
Applications with one major study only	51%	41%	P = 0.61
Number of list of questions during the CP*	2.0±0.6	1.9±0.8	P = 0.64
Time to answer to first LoQ (CP)*	113±75 days	128±89 days	P = 0.54

* Mean ± SD

It is obvious from the data included into Table 13 that the selected OMPs adequately represent all authorized orphan drugs.

Due to the complexity of approximately 170 non-orphan medicinal products authorized in the list of EPARs (including generic applications, etc) no such analysis was performed for non-orphans. In addition, the question here is less urgent as similar projects were compared to a representative selective of OMPs. If these non-OMPs are representative of all drugs is not of relevance for this analysis. In any case, such procedure ensures that class effects (e.g. if particular products are faster or slower authorized than others) cannot interfere with the analysis.

Number of Studies and Patients

The general problem in the development is the number of patients available. Inherently, patients suffering from orphan conditions are rare. For this reason, the number of patients included and the number of pivotal (main) studies performed shall be analysed for orphan and non-orphan medicinal products.

Table 14: Overview of the number of studies and patients included and comparator used during the development of orphan medicinal products (selected OMPs highlighted in grey)[72] [73]

OMP	Active Ingredient	Therapeutic Field	Number of Patients[74]	Number of Studies[75]	Comparator
Aldurazyme	Laronidase	Metabolic	55	1	Placebo
Atriance	Nelarabine	Oncology	109	2	Uncontrolled
Busilvex	Busulfan	(Oncology)	158	3	Uncontrolled
Celplene	Histamine hydrochloride	Oncology	n.a.	n.a.	n.a.
Cystadane	Betaine	Metabolic	202[76]	n.a.	--
Diacomit	Stiripentol	CNS	64	2	Placebo
Elaprase	Idursulfase	Metabolic	58	1	Placebo
Evoltra	Clofarabine	Oncology	40	1	Uncontrolled
Exjade	Deferasirox	Metabolic	591	1	Comparator
Fabrazyme	Agalsidase beta	Metabolic	58	1	Placebo
Firazyr	Icatibant	-	141	2	Placebo or active comparator
Gliolan	5-aminolaevulinic acid hydrochloride	Onclology	415	1	Control[77]
Glivec	Imatinib	Oncology	1,085	3	Active comparator
Increlex	Mecasermin	Mucosceletal	76	4	Placebo or uncontrolled
Inovelon	Rufinamide	CNS	139	1	Placebo
Litak	Cladribine	Oncology	63	1	Uncontrolled
Myozyme	Alglucosidase alpha	Metabolic	54	1[78]	Uncontrolled
Naglazyme	Galsulfase	Metabolic	39	1	Placebo
Nexavar	Sorafenib	Oncoloy	903	2	Placebo
Onsenal	Celecoxib	-	83	1	Placebo
Orfadin	Nitisinone	Metabolic	207	1	(Historical control)

[72] The following products were not included: Carbaglu, Siklos, Pedea and Lysodren as these drugs were authorized at least to a substantial part on the basis of data derived from literature

[73] Data derived from Summary for the Public (EPAR)

[74] Finalized main studies in the targeted indication.

[75] Main studies only: supportive studies and open-label extension studies not included.

[76] Literature data only

[77] As the mode of action is to visualize tumor tissue upon irradiation in the study fluorescent light is compared to white light

[78] Commitment of the sponsor to carry out randomized double blind studies.

PhotoBarr	Porfimer sodium	Oncology	208	1	Placebo/untreated
Prialt	Ziconotide	CNS	1,389	6	Placebo
Replagal	Agalsidase alpha	Metabolism	41	2	Placebo
Revatio	Sildenafil	CV	277	1[79]	Placebo
Revlimid	Lenalidomide	Oncology	704	2	Placebo
Savene	Dexrazoxane	Antidote	80	2	Uncontrolled
Soliris	Eculizumab	Haematology	88	1	Placebo
Somavert	Pegvisomant	Mucoscleletal	158	2	Placebo
Sprycel	Dasatinib	Oncology	1,104	6	Uncontrolled
Sutent	Sunitinib	Oncology	312 + 750	1 + 1	Placebo
Tasigna	Nilotinib	Oncology	438	2	Uncontrolled
Thalidomide Pharmion	Thalidomide	Oncology	1123	3	Placebo or active comparator
Thelin	Sitaxentan sodium	CV	516	3	Placebo, (comparator)[80]
Torisel	Temsirolimus	Oncology	626	1	Active comparator
Tracleer	Bosentan	CV	177	2	Placebo
Trisenox	Arsenic trioxide	Oncology	52	2	Uncontrolled
Ventavis	Iloprost	CV	201	1	Placebo
Volibris	Ambisentan	CV	394	2	Placebo
Wilzin	Zinc acetate	Metabolic	148	1	Uncontrolled
Xagrid	Anagrelide	Oncology	997	3	Uncontrolled
Xyrem	Sodium oxybate	CNS	246	2	Placebo
Yondelis	Trabectedin	Oncology	266	1	Uncontrolled
Zavesca	Miglustat	Metabolic	28	1	Uncontrolled

Accordingly, on average 1.84 ± 1.20 major or pivotal studies were submitted for authorisation of orphan medicinal products. In nearly every second case the use in the treatment of the orphan condition was justified on the basis of one major study only (51%, 22/42; 95% CI [30%; 74%]). Very similar figures result from the analysis of the selected orphan products (highlighted in grey in the table: 1.84 ± 1.14 major studies per drug and one such study only in 41% of all cases (7/17; 95% CI [11%; 72%]).

In 30%/29% (12/40 in all studies and 5/17 in the selected studies) of all cases no control group at all was included in the pivotal studies. This is particular frequent in the development of drugs intended for use in oncology where for as much as 60% of all drugs neither active comparator nor placebo groups were included into development (9/18). In most studies a placebo control is included whereas comparison with an active comparator is only rarely performed (8%; 3/40). In several of these cases, it appears that an adequate active comparator was available, e.g. retinoic acid in the development of arsenic trioxide,

[79] In one study sildenafil/placebo were used as add-on therapy to epoprostenol.

[80] In one study only an open-label bosentan arm was included

INFα in the development of cladribine, indomethacin for ibuprofen, hydroxyurea for anagrelide etc (Joppi et al., 2006).

Such analysis has also been performed for the reference products. An overview is presented in the table below.

Table 15: Details on pivotal studies during the development of the reference products.[81]

Reference Product	Active Ingredient	Therapeutic Field	Number of Patients*[82]*	Number of Studies*[83]	Comparator
Aclasta	Zoledronic acid	Mucoscleletal	357	2	Active comparator
Adenuric	Febuxostat	Metabolic	1,834	2	Active comparator and placebo
Circadin	Melatonine	CNS	820	3	Placebo
Cyanokit	Hydroxocobalamin	Antidote	98	2	Uncontrolled
Exforge	Amlodipin + valsartan	CV	5182	5	Active comparator and placebo
Extavia	Interferon-β1b	Immunologic	2,482[84]	3	Placebo
Galvus	Vidagliptin	Metabolic	4,977	9	Placebo and active comparator
Lyrika	Pregabalin	CNS	3,100	12	Placebo
Kinzalkomb	Telmisartan + hydrochlorthiazide	CV	818	2	Placebo or active comparator
MapCampath	Alemtuzumab	Oncology	148	3	Comparator or uncontrolled
Rasilez	Aliskiren	CV	11,944	17	Active comparator or placebo
Temodal	Temozolomide	Oncology	553	4	Comparator treatment or uncontrolled
Tarceva	Erlotinib	Oncology	731	1	Placebo
Tyveb	Lapatinib ditosylate	Oncology	408	1	Placebo
Velcade	Bortezomib	Oncology	256	2	Uncontrolled
Zevalin	Ibritumomab tuixetan[85]	Oncology	143	3	Placebo or active comparator
Zonegran	Zonisamide	CNS	351	4	Placebo

In contrast to the orphan products the number of pivotal studies submitted for initial marketing authorisation is on average twice as high for the non-orphan reference products: 4.41 ± 4.18 studies (mean ± SD). If these figures are compared to all authorized products

[81] Vimpat (lacosamide) was excluded as the EPAR was not published yet (August 2008).

[82] Finalized studies in the targeted indication according to the PSO.

[83] Main studies only: supportive studies and open-label extension studies not included.

[84] According to the summary for the public

[85] ^{90}Y-Radiolabeled antibody is clinically used

and the selected orphan medicinal products a significant difference between the means of 2.6 becomes obvious (two sided Student's t-test: P = 0.023 for both comparisons).

The direct comparison of orphan and reference products as presented in Table 16 clearly demonstrates that in only one case more major studies were performed for the authorisation of an OMP compared to the corresponding non-orphan product (Nexavar versus Tyverb). Interestingly, the non-orphan product was granted conditional approval meaning the product was authorized with incomplete clinical data. In three cases there was no difference in the study number and for all remaining products the study number was higher for the reference products. Similar to the figures calculated above the mean of the difference amounts 2.6 studies more being performed for the non-orphan products. However, the large extent is also due to the high number of studies included for the authorisation of Rasilex (N = 17). But even if this study package is excluded the mean difference and the difference of the means is slightly below two supporting the overall conclusion.

For the reference products, only for two of 16 products where such information was available only one main study was included (12.5%). Interestingly both products are intended for oncological use. Compared to the orphan products it appears that uncontrolled studies are more than twice as frequent but this difference is not significant most likely due to the low number of cases (Fischer's exact test P = 0.22 and P = 0.16).

In the direct comparison it becomes obvious that in 56% (9/16) of all studies orphan and reference product included one comparator – placebo or active substance, whereas in 31% (5/16) the level of reference treatments was higher for non-orphan drugs.[86] In conclusion, in 88% reference product at least one comparator was included (15/17). The level of quality with regards to this parameter is therefore typically much higher for non-orphan drugs compared to OMPs (12/40=30% and 5/16=31% for all orphan or selected orphan drugs; not significant: Fischer's exact test P = 0.10 and P = 0.16). In fact, both non-orphan products where no control group was included during analysis (Cynanokit and Velcade) are used for the treatment of severe and rare, i.e. most likely orphan conditions. For this reason, the same basic parameters apply here as for "normal orphans". The frequent use of active comparators during the development of non-orphan medicinal products is most likely also driven by marketing strategy. In particular if widespread diseases are treated with several therapy options, such as diabetes or hypertension, phase III studies are typically designed in a way that the results also allow a positioning on the market.

Table 16: Selected orphan and reference products: Differences in number of main studies and comparator groups.[87]

Orphan Product	Reference Product	Therapeutic Field	Difference No. of Studies[88]	Comparator Orphan	Comparator Reference
Somavert	Aclasta	Mucoscleletal	0	Placebo	Active comparator
Xyrem	Circadin	CNS	0	Placebo	Placebo
Savene	Cyanokit	Antidote	0	Uncontrolled	Uncontrolled
Thelin	Exforge	CV	2	Placebo	Active comparator and placebo
Soliris	Extavia	Immunologic	2	Placebo	Placebo

[86] Placebo or active comparator is regarded as higher level compared to uncontrolled studies and placebo and active comparator is regarded as higher level compared to only either of both.

[87] Adenuric and Cytadane were excluded as Cystadane was authorized on the basis of efficacy data derived from published literature.

[88] A positive figure indicates that the number of main studies for the non-orphans was larger than for orphan drugs and a negative figure for the reverse.

Zavesca	Galvus	Metabolic	8	Uncontrolled	Placebo and active comparator
Prialt	Lyrika	CNS	6	Placebo	Placebo
Tracleer	Kinzalkomb	CV	0	Placebo	Placebo or active comparator
Trisenox	MapCampath	Oncology	1	Uncontrolled	Active comparator
Volibris	Rasilez	CV	15	Placebo	Active comparator
Yondelis	Temodal	Oncology	3	Uncontrolled	Comparator treatment or uncontrolled
Sutent	Tarceva	Oncology	0	Placebo	Placebo
Nexavar	Tyverb	Oncology	-1	Placebo	Placebo
Revlimid	Velcade	Oncology	0	Placebo	Uncontrolled
Litak	Zevalin	Oncology	2	Uncontrolled	Placebo or active comparator
Inovelon	Zonegran	CNS	3	Placebo	Placebo

Overall, the data package prepared for the authorisation of non-orphan medicinal products appears to be more comprehensive compared to orphan products. In particular, normally more studies are performed for non-orphan drugs compared to OMPs. In addition, it is not uncommon to include no control group in the development of orphan drugs. This has most likely several causes:

- The limited number of patients does not allow performing huge studies with a justifiable effort.
- Per definition orphan conditions cannot be treated adequately. For this reason it is frequently observed that there is no appropriate therapy for the indication. As orphan conditions are severe diseases in many cases the use of a placebo cannot be justified for ethic reasons. This factor appears to be of particular relevance for oncologic products. In conclusion, compared to non-orphan drugs no control groups at all might be in cases feasible.
- Due to the fact that there is no adequate treatment for orphan conditions and due to the fact, that these diseases are severe, the request to demonstrate a favourable risk/benefit ratio appears easier to achieve compared to many non-orphan conditions.

However, these arguments might explain some of the differences but not all. For instance, in none of the development packages for treatment of PAH an active comparator control was included despite the fact that an increasing number was available. This can be exemplified by Volibris: when orphan designation was sought for this drug Tracleer as the first OMP in this indication had been authorized for years.

The data presented in Tables 14 and 15 allow also direct comparing the details in the development of orphan and non-orphan medicinal products with regards to patients included into development.

Table 17: Comparison of the number of patients included in the development of orphan and non-orphan medicinal products.

Orphan Product	Reference Product	Therapeutic Field	Patients (Orphan)	Patients (Non-orphan)	Ratio
Somavert	Aclasta	Mucosceletal	158	357	1.3
Cystadane	Adenuric	Metabolic	202	1,834	9.4
Xyrem	Circadin	CNS	246	820	3.3
Savene	Cyanokit	Antidote	80	235	2.9
Thelin	Exforge	CV	516	5,182	10.0
Soliris	Extavia	Immunologic	88	2,482	28,2
Zavesca	Galvus	Metabolic	28	4,877	174
Prialt	Lyrika	CNS	1,389	3,100	2.2
Tracleer	Kinzalkomb	CV	177	818	4.6
Trisenox	MapCampath	Oncology	52	148	2.8
Volibris	Rasilez	CV	394	11,944	30.3
Yondelis	Temodal	Oncology	266	553	2.1
Sutent	Tarceva	Oncology	531[89]	731	1.4
Nexavar	Tyverb	Oncology	971	408	0.4
Revlimid	Velcade	Oncology	708	256	0.4
Litak	Zevalin	Oncology	63	142	2.3
Inovelon	Zonegran	CNS	139	351	2.5

If data from this comparison are analysed it becomes obvious that on average data of 5.5-times more patients were included into the authorisation request of non-orphan medicinal products compared to orphan drugs. This figure results from a meta-analysis (6,068 orphan patients and 33,508 non-orphan). However, if this analysis is stratified to the different therapeutic fields the result becomes more differentiated:

- In oncology the figures are very similar (2850/3845 = 0.9; range 0.4 – 2.8). This is in part due to the fact that several of the selected non-orphan medicinal products are authorized in orphan conditions, such as Velcade in multiple myeloma, MapCampath for CLL or Temodal in the treatment of glioma[90]. Alternatively the authorized indication comprises subsets which can also be regarded being orphan but are not recognized by the COMP as outlined above in great detail (e.g. radiolabeled ibritumomab for the treatment of follicular B-cell non-Hodgkin's lymphoma[91]).
- For the authorisation of CNS drugs overall two- to threefold more patients are included in authorisation dossiers for non-orphan drugs compared to orphans (1774/4271 = 2.8; range 2.2 to 3.3).
- Large differences of more than one order of magnitude are observed in drugs for the treatment of cardiovascular or metabolic diseases (Metabolic: 220/6,711 = 29.2; CV: 1,087/17,944 = 16.5).

[89] Development in GIST and RCC

[90] Temodal was authorized prior to the European orphan regulation. The famous statement alledged to Michail Gorbachev "Those who are late will be punished by the life itself" is not true in this case – being early was a disadvantage.

[91] Zevalin is in fact authorized as an orphan drug in the USA where definition of subsets is not judged being critical as in the EU

In conclusion, differences between orphan and non-orphan medicinal products in the development efforts strongly depend on the therapeutic field. In oncology and to a smaller extent in the treatment of CNS diseases appears to be comparable whereas the development packages for metabolic and CV diseases are much more extensive for non-orphan drugs. It can therefore be concluded that regulatory guidance and general strategies for the development of oncologic products can be applied no matter if the condition is orphan or not. In addition, in hereditary metabolic orphan diseases – typically characterized by deficiency in a particular gene product – in most cases less than 100 patients are required to sufficiently prove efficacy for authorisation.

Statistical Significance

For evident reasons low number of patients available makes it more challenging to reach statistical significance with regards to the primary or any secondary endpoint in the pivotal studies for orphan medicinal products. The table below comprises an overview of the primary endpoints of the main studies and the significance of the outcome. The data are derived from the Scientific Discussion of the EPAR.

Table 18: Outcome and statistical significance of the primary objective in the pivotal clinical trials during development of orphan drugs (data with non-orphan reference products are highlighted in grey)[92]

OMP	Active Ingredient	Therapeutic Field	Primary Objective	Outcome	Significance
Aldurazyme	Laronidase	Metabolic	FVC[93]	5.9 percentage points compared to placebo	P = 0.016
			6-min-walk test	Δ=38.1 m compared to placebo	P = 0.066
Atriance	Nelarabine	Oncology	Complete response	33%/18% responder	NA*
Busilvex	Busulfan	(Oncology)	Time to engraftment	11 ± 3 and 15 ± 4	NA*
Diacomit	Stiripentol	CNS	50% seizure reduction	71.4%/66.7% responders compared to 5%/9.1% in placebo group	(significant)
Elaprase	Idursulfase	Metabolic	FVC and 6-min-walk test	(not reported)	"borderline significance"
Evoltra	Clofarabine	Oncology	Overall remission	20%	NA*
Exjade	Deferasirox	Metabolic	Success rate liver iron content	53% compared to 66% deferioxamine	(n.s.)

[92] Several drugs are excluded from this analysis as their clinical efficacy was mainly or exclusively based on data derived from scientific literature. These products include Lysodren, Siklos, Pedea,Carbaglu and Cystadane.

[93] Forced vital capacity

Fabrazyme	Agalsidase beta	Metabolic	Reduction in GL-3 accumulation	62% compared to 7% in the placebo group score of zero	P < 0.001
Firazyr	Icatibant	-	Onset of relive of symptoms	2.0/2.5 h compared to 12 h tranexamic acid and 4.6 h placebo	P < 0.001 (active) P = 0.14 (placebo)
Gliolan	5-Aminolevulinic acid	Oncology	Percentage of patients without residual tumor[94]	63.6% versus 37.6% control	P < 0.0001
Glivec	Imatinib	Oncology	Complete and partial response or heamatologic response	38% CR + PR and 26%-88%[95]	NA*
Increlex	Mecasermin	Mucosceletal	Linear growth or growth rate	Improved height velocity compared to pretreatment	P < 0.0001
Inovelon	Rufinamide	CNS	Total seizure frequency	32.7% reduction compared to 11.7% in placebo group[#]	P = 0.0015
Litak	Cladribine	Oncology	Complete remission	76%	NA*
Myozyme	Alglucosidase alpha	Metabolic	(not formally evaluated)	(not formally evaluated)	(not formally evaluated)
Naglazyme	Galsulfase	Metabolic	12 min-walk test	Δ = +92±40 m compared to placebo	P = 0.025
Nexavar	Sorafenib	Oncology	Progression free survival	167 days sorafenib vs. 84 days placebo	P < 0.00001
Onsenal	Celecoxib	Oncology	Reduction in colorectal polyp number.	28.0% reduction compared to 4.5% placebo	P = 0.001
Orfadin	Nitisinone	Metabolic	Survival	Two year: 96%	ND*
PhotoBarr	Porfimer sodium	Oncology	Complete response	76.8% compared to 38.5% control	P < 0.0001
Prialt	Ziconotide	CNS	Change in VASPI[96]	53%/31% ziconotide vs. 18%/6% days placebo[97]	P < 0.001 (both studies)

[94] Contrast enhancing tumor seen on early postoperative MRI

[95] Depending on study – different degrees of disease severity or doses.

[96] Visual Analogue Scale of Pain Intensity

Replagal	Agalsidase alpha	Metabolic	Serious debilitating pain	(decline in pain)	P = 0.021
Revatio	Sildenafil	CV	6 min-walk test	+45.3 m compared to baseline	P < 0.0001
Revlimid	Lenalidomide	Oncology	Time to progression	48/49 weeks lenalidomide vs. 20/20 weeks placebo	P < 0.001 (both studies)
Savene	Dexrazoxane	Antidote	Avoid surgical intervention	100%/97.2%	NA*
Soliris	Eculizumab	Haematologic	Hemoglobin stabilitsation Packed red blood cell transfusion	43% of patients vs. 0% placebo 0% of patients vs. 10% placebo	P < 0.001 P < 0.001
Somavert	Pegvisomant	Mucosceletal	Suppression in IGF-I concentration	-62.5% vs. -4.0% placebo	P = 0.0001
Sprycel	Dasatinib	Oncology	Cytogenic response	27%-80% depending on the patient population	NA*
Sutent	Suitinib	Oncology (MRCC) Oncology (GIST)	Overall response rate Time to progression	ORR = 36% Median TTP 27.3 versus 6.4 weeks placebo (HR=0.33)	NA* P < 0.001
Tasigna	Nilotinib	Oncology	Major cytogenic response[98] Complete haematologic response	48.8% 42%	NA* NA*
Thalidomide Pharmion	Thalidomide	Oncology	Overall survival TTP	15-21 months compared to active comparator 98 versus 28 weeks placebo	Significant P < 0.0001
Thelin	Sitaxentan sodium	CV	6-min-walk test	<u>Study 1:</u> Δ = 35.0 m compared to placebo <u>Study 2:</u> Δ = 31.4 m compared to placebo	P = 0.006 P = 0.03

[97] Data from a third main study submitted during evaluation process not included.

[98] Defined as partial and complete response

				Study 3: [99]Δ = 24.3 m compared to placebo	P = 0.21
Torisel	Temsirolimus	Oncology	Overall survival (median)	10.9 m temsirolimus compared to 8.4 m tem/INF or 7.3 m INF	P = 0.008
Tracleer	Bosentan	CV	6-min-walk test	Δ = 44.2 m compared to placebo	P = 0.0002
Trisenox	Arsenic trioxide	Oncology	Rate and duration of complete remission	87% of the patients achieved CD within a median time of 57 days	NA*
Ventavis	Iloprost	CV	(Composite endpoint)[100]	17% responders compared to 5% placebo	P = 0.007
Volibris	Ambrisentan	CV	6-min-walk test	31 m increase from baseline (placebo corrected)	(significant)
Wilzin	Zinc acetate	Metabolic	(no primary objective)	(no data)	(no data)
Xagrid	Anagrelide	Oncology	Complete or partial response	Depending on study 82%, 79% or 60% CR, 6%, 8% or 10% PR	NA*
Xyrem	Sodium oxybate	CNS	Change in total number of cataplexy attacs	Study 1: -16.1 vs. -4.3 placebo Study 2: 0 vs. +11 placebo	P = 0.0008 P < 0.001
Yondelis	Trabectedin	Oncology	Time to progression	Median TTP 3.8 months[101]	NA*
Zavesca	Miglustat	Metabolic	Organ volume response (MRT or CT)	Mean reduction from baseline of liver volume 14.5% and of spleen volume 26.4%	P < 0.001 (both studies)

* No comparator included.

[99] Patients with lesser disease severity compared to the other studies

[100] Improvement in exercise capacity AND improvement by at least one NYHA class AND no deterioration or PAH or death.

[101] In the recommended schedule of once every three weeks compared to 2.1 months for those receiving Yondelis three times per months.

In conclusion, for most orphan medicinal products statistic significance was reached in at least one main study (if significance is defined as a type 1 error probability of less than 5%) independent of the question if all OMPs or if selected products are analysed only. However, many studies did not include any control group as outlined in the previous section. Evidently, in cases where response rates or other parameter that cannot be compared to baseline levels no significance analysis is possible. This includes in particular products intended for oncology where complete or partial response are frequently the endpoints. In addition, most of these products have no control group (which is true for orphans and non-orphans but more pronounced in OMPs as outlined in the previous section). In fact, significance information is available only for 41% (7/17) of the oncological orphan products.

In those projects where a statistical analysis could be performed only one OMP was obvious with a P-value higher than 0.05 for a primary parameter: Exjade (deferasirox), an iron chelator that is authorized for treatment of chronic iron overload. In the pivotal study no non-inferiority was demonstrated with the comparator product deferoxamine (53% compared to 66% response). From a post-hoc subgroup analysis for 381 patients who had particularly high levels of iron in their liver the non-inferiority criteria were achieved. On the basis of these data the efficacy was justified. The decision on the authorisation of Exjade was in part based on the fact that it can be used in young children or patients receiving less frequent infusions where the application of deferoxamine is not possible or inadequate.[102]

If analysis was focused on comparative trials no orphan product was authorized where no significance compared to placebo was obtained with regards to a primary endpoint. For Firazyr (icatibant) no significance was obvious in the direct comparison with the placebo groups rather than a trend of improvement (P = 0.14) but compared to tranexamic acid, a comparator authorized in some countries, the benefits were significant (P < 0.0001). In addition, Firazyr was superior to both comparators with regards to several secondary endpoints.

To compare the orphan and non-orphan products, in the table below the same analysis for the reference products is presented.

Table 19: Outcome and statistical significance of the primary objective in the pivotal clinical trials during development of the defined reference medicinal products.

OMP	Active Ingredient	Therapeutic Field	Primary Objective	Outcome	Significance
Aclasta	Zoledronic acid	Mucoscleletal	Proportion of responders[103]	0.95/0.97 responders compared to 0.75/0.73 in placebo group Risedronate	P < 0.0001 (both studies)
Adenuric	Febuxostat	Metabolic	Serum urate <6 mg/dl	65%/79% febuxostat compared to 0%/1% placebo and 22%/39% active comparator	P < 0.001

[102] Interestingly, deferoxamine is also authorized for the use in children.

[103] Normalisation of serum alkaline phosphatase or reduction by at least 75%

Circadin	Melatonin	CNS	Quality of Sleep Response rate	<u>Study 1:</u> Compared to placebo Δ = 6.0 mm <u>Study 2:</u> 26% vs. 15% placebo	P = 0.047 P = 0.014
Cyanokit	Hydroxo-cobalamine	Antidote	Survival	Overall 73% of all patients survived	NA*
Exforge	Valsartane + amlodipine	CV	Change in MSDBP	Significant decrease from baseline, superior to placebo and similar to comparator	(significant)
Extavia	Interferon β-1b	Immunologic	n.a.	n.a.	(significant)[104]
Galvus	Vildagliptin	Metabolic	Change in HbA_{1c}	<u>Monotherapy</u> superior to placebo and inferior to comparator <u>Add-on therapy</u> Significant decrease	(significant)
Lyrika	Pregabalin	CNS	Mean pain score at end-point[105]	Compared to placebo Δ = -0.18 to -1.57 (300 mg) Δ = -0.64 to -2.02 (600 mg)	(significant except for one of eleven studies)
Kinzalkomb	Telmisartan + hydrochloro-thiazide	CV	Seated through DBP	-3.5/-3.8 mm Hg versus active comparator	(significant)
MapCampath	Alemtuzumab	Oncology	CR + PR	Depending on study 28%-33%	NR*
Rasilez	Aliskiren	CV	Change in msDBP[106]	Mean decrease of 1.5 to 4.5 mmHg compared to placebo[107]	(except for one study always P < 0.05)

[104] Currently no assessment report available. Information collected from the summary for the public.

[105] Based upon an 11 point numerical rating pain scale. Mean pain score at entry was defined as the mean score for the last 7 available pain diary entries while the patient was on study medication.

[106] Mean sitting diastolic blood pressure

[107] Data for combination therapy also available

Temodal	Temozolomide	Oncology	PFS at 6 months	Study 1: 21% vs. 8% in the procarbazin group Studies 2/3: 19% and 46%[108]	P = 0.008 (Study 1) Studies 2/3: NA*
Tarceva	Erlotinib	Oncology	Overall median survival	6.7 months vs. 4.7 months placebo	P = 0.001
Tyverb	Lapatinib ditosylate	Oncology	Time to progression	Median TPP 27.1 weeks for combination with capecitabine vs. 18.6 weeks for capecitabine Hazard ratio: 0.57	P = 0.00013
Velcade	Bortezomib	Oncology	Overall response rate (ORR)[109]	35% and 33-50% (depending on dose)[110]	NR*
Zevalin	Ibritumomab tiuxetan	Oncology	Overall response rate (ORR) [111]	73% compared to 47% active comparator[112]	P < 0.002
Zonegran	Zonisamide	CNS	Change of seizure frequency from baseline	Compared to base line median reduction of 38.5% or 46.1% (300 or 500 mg/d)	P = 0.0034 (300 mg) or <0.0001 (500 mg) Placebo and not significant

In summary, for all reference products significant benefit was demonstrated in at least one main study. Exception are Velcade and MapCampath (two product authorized for oncological orphan conditions) where no comparator was included into the main studies.

The conclusion from this analysis is obvious: Significant improvement in a primary endpoint is common practice for orphan medicinal products as for non-orphan drugs. It appears that a non-significant positive trend cannot be justified on the basis of the limited number of patients. However, as outlined in the previous section, in many cases no reference treatment is available. In such cases frequently no formal significance analysis is feasible. This includes for instance diseases where no change from baseline can be determined as for instance in most trials on the development of therapies in oncology.

[108] Study 1 and 2 included patients with glioblastoma multiforme, study 3 patients with anaplastic astrocytoma.

[109] Defined as Partial Response (PR) + Complete Remission (CR) + Minimal Response (MR)

[110] Two additional comparative studies were ongoing at the time of submission

[111] Defined as Partial Response (PR) + Complete Remission (CR) + Clinical Complete Remission (CCR)

[112] Data from two uncontrolled trials: ORR = 67% and 59%

Data used for this analysis are derived from EPARs of the medicinal products taken into consideration. It is recognized that these report are regularly updated. Accordingly, in particular in those indications where the product was authorized under exceptional circumstances the development is ongoing after authorisation. It may be that the data in the EPAR do not reflect the data at the time of authorisation due to the ongoing development process. For these drugs it is accepted by the EMEA that the rarity of the disease prohibits its proper development. It cannot be excluded that at the time of authorisation no significant benefit was obvious and that authorisation was based on a trend detected at an interim analysis. Such cases would have no major impact on the overall conclusion that it should be aimed at significance for several reasons: Products that are authorized under exceptional circumstances and where no significance was obvious reflect only a minority of all orphan products. Second, no such OMP was identified where the data that were still awaited included demonstration of significance with regards to a primary endpoint. It is unlikely that no case is detected where the awaited data comprised demonstration of significance if this was a prominent feature for these drugs. Last but not least, sooner or later even for such drugs significance was demonstrated as is obvious from Table 18. This means that the studies have to be prepared and presented in a way that allows detecting significance sooner or later and authorisation must have been based on at least a clear trend on the data from an interim analysis.

Surrogate endpoints are frequently observed as primary parameters in the development of orphan drugs as well as non-orphans rather than hard endpoints (e.g. responder fraction in oncological development rather than survival of patients, six-minutes walking test in PAH and other conditions etc). This is worth being noted as the “Small Population Guideline” recommends the use of hard endpoints.

Summary and Conclusion

As one would expect overall the study efforts during the development of non-orphan products are much higher than for orphans. Whereas in many orphan programs only one or two main studies are performed the number of studies is on average twice as high for non-orphan products. Similarly, in the development of the latter higher numbers of patients are included but this figure varies significantly with the disease area. For instance, the difference is marginal for oncological projects whereas it is pronounced for metabolic diseases.

One of the major differences between orphan and non-orphan products is that it is frequently seen in the development of the former drugs that no control group is included, in particular in the field of oncology. Except for these cases, independent of the question if an orphan drug is developed statistical significance for at least one primary endpoint in at least one main study should be achieved. For the authority it is easier to accept an underpowered study than not achieving significance if sufficient patients had been available.

The Significant Benefit Claim

As outlined in the section on the orphan designation, providing sufficient evidence for significant benefit is one of the most important aspects that has to be considered[113]. This claim is also applicable for diseases where no pharmacological therapy is authorized at the time of submission of the MAA. However, this is normal situation for most orphan diseases. Significant benefit is one of the criteria that have to be fulfilled for an (authorized) orphan drug.

Whereas in the designation process the possibility for such benefit has to be reasonably demonstrated it has to be argued in parallel to the CHMP review that this assumption is really valid (this is done as part of the maintenance procedure outlined above).

[113] Regulation (EC) 141/2000, Article 3 (1) b).

The term significant benefit has been defined in more detail in Article 3 (2) of Regulation 847/2000 (see also above): *clinically relevant advantage or a major contribution to patient care*". Such advantage could be greater efficacy, an improved safety profile, improved pharmacokinetic properties, compliance promoting features, or evidences to show fewer interactions with food or medicinal products.

Against this background it is striking that such provisions appear to be no major hurdle in the authorisation process: It has already been mentioned that in total five orphan medicinal products are available for the treatment of class III pulmonary arterial hypertension. In all development programs the studies were performed placebo-controlled rather than using an active comparator as control against one of the already authorized OMPs. To a certain extent this might be due to timing as a potential comparator might not have been authorized or available at the time clinical development was planned. However, from a pure formal sense this should be irrelevant as significant benefit is a *conditio sine qua non* for orphan drugs. In such case one would expect that the product gets authorized but not as an orphan drug.

In the EPARs of the treatments for pulmonary arterial hypertension the question of significant benefit is at most superficially discussed (in striking difference to similarity which is addressed in most cases very clearly). However, the EPAR is issued by the CHMP and the analysis for significant benefit is done by the COMP and summarized in a final report. Still with regards to treatments for PAH in most cases no reasoning was obvious from reviewing the data presented in the EPAR justifying or clearly demonstrating a significant benefit as defined in Regulation 847/2000:

- No information was detected justifying why Ventavis might provide a significant benefit for PAH patients. The drug product is a nebulizer solution. It is not evident if this is a benefit compared to tablets (the pharmaceutical form of other PAH inhibitors) or not. On the one hand such drugs for inhalation typically have usually much lower amounts of active substance compared to oral formulation which frequently results in less systemic side effects. On the other hand the application is much more demanding compared to swallowing a tablet which might result in impaired compliance.
- In the EPAR for Revatio (sildenafil) no superiority compared to any other treatment of PAH was mentioned. This drug can be used in combination with the (non-orphan) treatment epoprostenol but a direct benefit for the patients resulting from such combination was not outlined. In addition, in one published study Revatio and Tracleer were directly compared. In this trial, no difference with regards to safety and efficacy was obvious (Wilkins et al., 2005).
- In the development of Thelin (sitaxentan sodium) an active orphan comparator was included. One study comprised an open label reference arm where the patients were treated with bosentan (Tracleer). Overall neither efficacy nor safety appeared to differ between boths drugs and it was concluded that the risk/benefit ratio was comparable to bosentan. It is furthermore stated that no benefit over sildenafil is expected. However, in one supportive study patients who have failed prior bosentan treatment were treated with sitaxentan. Due to small size and lack of comparator group no compelling evidence was demonstrated that the drug might be active in the treatment of refractory patients.
- The authorized indication for Volibirs (ambrisentan) comprises also patients suffering from class II PAH. It has to be noted that according to the EPAR there was "concern about representativeness of class II patients". However, the authorisation can be justified in this disease area. Still, no reasoning providing significant benefit over all other drugs in the treatment of class III patients was obvious from the EPAR.

In conclusion, there is weak evidence that Thelin might be active in patients that were responding appropriately to bosentan. Such argumentation for other drugs that were authorized at that time was not provided (i.e. potential benefit over Ventavis or Revatio). The authorisation of Volibris can be explained as so far untreated patients – suffering from class II disease – were included. In all other cases no reasoning supporting a significant benefit was obvious. In contrast, it is at several occasions mentioned that the different products were comparable in safety and efficacy.

Another example where two orphan products were authorized in the same therapeutic indication includes the bcr/abl kinase inhibitors Tasigna and Sprycel. Both are active in the treatment of CML patients not responding adequately to imatinib (Glivec), another orphan product with the same mode of action. Due to the fact that both drugs act against imatinib-resistant patients, the benefit compared to that OMP is obvious. However, there is no obvious information with regards to a clinical benefit of Tasigna (nilotinib) over Sprycel (dasatinib) that was authorized one year earlier. Both drugs have roughly the same potency but no direct comparison is available. The same is true for safety features albeit it appears that the problem of QT prolongation is more pronounced for Tasigna (i.e. the later authorized product). Both drugs are active against a wide pattern of mutations of the target kinase with the same exception, lack of activity against the T513I mutation. However, in one comparative trial published in July 2007 (i.e. prior to authorisation of Tasigna) it was demonstrated that dasatinib can be active in the treatment of patients not responding adequately to nilotinib (Quintas-Cardama et al., 2007). No such information was identified for nilotinib in the treatment of dasatinib-resistant CML but such effect cannot be excluded. Overall, no information was identified demonstrating a clear benefit for the patients for Tasigna compared to Sprycel.

In conclusion, there is no indication that lack of convincing data supporting the significant benefit had a major impact on the authorisation of OMPs. There are several cases where (non similar) orphan medicinal products were authorized in the same therapeutic indication with no obvious benefit for the patients as defined in regulation 847/2000. Furthermore, to our information there is no example so far where orphan authorisation was refused and converted into a “normal” authorisation as finally significant benefit was not demonstrated adequately.

However, it should be noted that potentially the significant benefit was justified on the basis of data that were for confidentiality reasons not included into the EPAR or were not directly obvious from the information provided.

Available Patients

It was furthermore investigated if the EPARs allow a conclusion on the absolute fraction or number of patients suffering from an orphan condition that might be available for clinical development. An overall analysis was performed by determining the fraction of patients suffering in the EU from an orphan condition for which an orphan drug is already authorized that were included into the main studies used to justify marketing authorisation in relation to all patients, i.e. the prevalence. In conclusion, this analysis revealed that less than one percent (0.7%) of all patients was included in the main studies (data not presented). However, such approach has some methodological weaknesses, first and most important here the authorized indication is set in relation to the orphan condition. As in most cases the indication is highly focused and the orphan condition is defined broadly such procedure is not valid.

To deal with this issue all orphan medicinal products were selected where the authorized indication is essentially identical to the orphan condition. An overview of these drugs is summarized in Table 20 below.

Table 20: Overview of orphan products with similar authorized indication and orphan condition

Product	Authorized Indication	Orphan Condition	Total Number of Patients[114]	Patients Included in Development	Ratio
Fabrazyme	For use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease	Treatment of Fabry's disease	750	73	9.7%
Myozyme	Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Pompe's disease	Treatment of Pompe's disease	6,500	35	0.5%
Naglazyme	Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysacchari-dosis VI	Treatment of Mucopolysaccharidosis, type VI (Maroteaux-Lamy Syndrome)	550	88	16%
Nexavar*	Treatment of hepatocellular carcinoma	Treatment of hepatocellular carcinoma	46,000	789	1.7%
Prialt	Treatment of severe, chronic pain in patients who require intrathecal analgesia	Treatment of chronic pain requiring intraspinal analgesia	58,000	1,449	2.5%
Replagal	For use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease	Treatment of Fabry's disease	750	66	8.8%
Savene	Treatment of anthracycline extravasation	Treatment of anthracycline extravasation	1,470	101	6.9%
Soliris	Treatment of paroxysmal nocturnal haemoglobinuria	Treatment of paroxysmal nocturnal haemoglobinuria	4,000	195	4.8%
Xyrem	Treatment of narcolepsy with cataplexy in adult patients[115]	Treatment of narcolepsy	157,250	505	0.3%

*extension application

In total 3,301 patients were treated for diseases which occur in 275,270 patients in the EU. This corresponds to a fraction of 1.2%. However, the variability is pronounced ranging

[114] This refers to all patients included during development and not only to main studies

[115] As cataplexy is observed as often as in 80%-90% of all cases

from 0.3% to 16%. On the other hand, many of the studies refer to severe and very rare metabolic diseases that are not fatal in a short time period. For this reason, the patients can be transferred to a specialized centre enabling such high inclusion of all available patients. As indicated, for Nexavar hepatocellular cancer is an extension application with most likely fewer patients compared to initial application. However, the data package comprises dose-range finding as well as a large pivotal study. As PK trials typically comprise only few patients no pronounced difference is expected compared to an initial application. If Nexavar is excluded from analysis a fraction of 1.1% results.

This approach has one major weakness. In case data are submitted from studies outside of the European Union the patients would still be calculated as European patients available for development. This results in an over- rather than an underestimation of the fraction of available patients.

In conclusion, it can be roughly estimated that no more than approximately one percent of all patients suffering from an orphan condition are available for development in the fields of an orphan disease. The range is pronounced and in particular in some metabolic diseases much higher levels can be achieved.

Summary

Compared to non-orphan products the development of OMPs is characterized and complicated by the limited number of patients available. There is no special procedure how to deal with this issue. The “Guideline on Clinical Trials in Small Populations” provides some guidance and measures which may help to maximize the information gain from clinical studies.

In general, the rarity of patients translates into some differences in the development of orphan drugs if compared to non-orphans. Overall fewer patients are included into the development and the overall number of pivotal studies is only half as high. In addition, frequently no control group is included at all whereas such designs are only rarely observed for non-orphan drugs. However, due to insufficient therapeutic options the lack of active control might be due to the fact that no adequate comparator is available and lack of placebo groups due to the fact that such mock-treatment might ethically not be acceptable for severe diseases.

Independent if an orphan or non-orphan product is developed it should be aimed at statistical significance for the primary endpoint. For OMPs one might justify an underpowered study as a consequence of lack of patients for proper development.

AUTHORISATION OF ORPHAN MEDICINAL PRODUCTS

Orphan medicinal products are generally qualified to be authorized under the centralized procedure. In fact, pursuing this pan-European way is obligatory for these products. The idea behind this is that all patients in the EU shall have the opportunity to benefit from this new product. Interestingly the regulation does not contain a formal obligation to distribute the product all over the EU.[116]

In general, the European legislation does not distinguish between orphan and non-orphan drugs in the marketing authorisation procedure (with the only exception that there is no formal eligibility procedure for the centralized procedure for orphan medicinal product apart from information only). In this section different authorisation types that might be of particular relevance for OMPs will be presented. In addition, it will be analysed that the differences between orphan and non-orphan products will be reflected in the overall course of the authorisation procedure.

Peculiarities in the Authorisation of OMP

As already outlined there is always a pronounced medical need for new therapies for orphan conditions. This is a clear contrast to non-orphan diseases. In this section it will be investigated if this medical need leads to an overall faster authorisation process of orphan products. In contrast, one could also argue that paucity of data due to the small number of patients available may lead to increased discussions or even decreased success during authorisation as the data tend to be less robust compared to non-orphan drugs.

Review Time

From time to time the expectation is expressed that the CHMP should also take the difficulties in the development of OMPs into consideration or that the CHMP should acknowledge the efforts of a pharmaceutical company to develop a medicinal product in a neglected disease area during its review. However, from a legal point of view the same principles apply for orphan medicinal products as for non-orphans: the drug has to be of appropriate quality, safe and efficacious.

Nevertheless it was investigated if there are any differences obvious in the authorisation procedure of orphan medicinal products compared to non-orphans. Such difference might be due to the fact that CHMP members feel being under moral pressure as there is urgent medical need for drugs against orphan diseases.

In a first step, the active review time of both classes of drugs was compared. The data are derived from the monthly reports of the CHMP plenary meetings. Focus was put on initial marketing authorisations. Informed consent and generic applications were excluded from analysis as well as appeal procedures. The data included comprise all drugs authorized via the centralized procedure in the time period December 2005 to July 2008.

A total of 93 medicinal products were authorized during this time (23 orphan medicinal products and 70 non-orphans). The mean active review time for the orphans was 197 ± 15.5 days and for non-orphan medicinal products 192 ± 18.6 days. The difference is not significant (two sided Student's t-test, $P = 0.21$). The fraction of drugs with a review

[116] Article 8 3. (c) suspends the similarity claim in cases "*the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product*". This could be interpreted as an indirect measure to ensure overall distribution. However, the role of parallel distribution is unclear for such considerations.

time of no more than 180 days was 22% (5/23) for OMPs and 26% (18/70) for non-orphans. This difference is also not significant (Fischer's exact test, P = 0.21).

In conclusion there is no difference in the active review time of orphan compared to non-orphan medicinal products.

List of Questions (LoQ)

In the centralized procedure a clock-stop is foreseen at day 90. The sponsor will obtain a consolidated list of questions. Upon receipt of his answer the clock is restarted. If not all issues are clarified additional outstanding questions might be raised by the CHMP.

The total number of such lists of questions during the initial marketing authorisation procedure were determined and compared between orphan medicinal products and non-orphan products. This figure is regarded as a kind of surrogate parameter for the complexity of an application assuming that more complex applications or applications based on data of minor quality will result in an increased number of lists of questions. It might also give some indication if an application is reviewed critically or if it is "waved through".

In general there was no application where not at least one list of questions was issued by the CHMP. On the average for orphan medicinal products 2.0 ± 0.6 LoQ were raised (n = 44). For selected OMPs (see Table 12) the mean number was 1.8 ± 0.4 (n = 17) and for the reference products 1.9 ± 0.8 (n = 17). The difference of orphan and non-orphan drugs (all orphans and selected orphans) is not significant (two sided Student's t-test: P = 0.65 and P = 0.32 respectively). A pair wise direct comparison of selected orphan and non-orphan reference products reveals that in 63% of all cases there is no difference between the number of LoQ and in 19% each orphans or non-orphans receive less LoQ than the other.

In conclusion, there is no difference between orphan medicinal products and non-orphan products with regard to the number of the lists of questions issued by the CHMP.

Answer Time to the First List of Questions

As mentioned in the previous section there is no authorized product that did not receive a list of question after the first CHMP review. In this approach, the time required by the applicant to respond to the first list of question was analysed. This time period can be regarded as kind of a surrogate parameter with regards to the question if serious issues are raised or if only minor questions have to be clarified. Of course, other factors might also contribute to such response times, for instance organisation, experience or capacities of the sponsor company.

Overall the mean (± SD) time for the first response is 113 ± 75 days for all orphan drugs and 128 ± 89 days for the selected OMPs. Compared to these times there is a trend of approximately two to four weeks shorter response time for the reference products (95 ± 56 days). However, the difference is not significant due to pronounced variability of data (two sided Student t-test P = 0.21 and P = 0.31 respectively). If the difference between the selected orphan drug and the assigned reference drug is calculated in a pair wise comparison, the mean review time is 24 days shorter for non-orphan drugs. Accordingly, these data indicate that on average the response time on the first list of questions was on average approximately three weeks shorter for non-orphan drugs compared to orphans.

Pursuing the same question, the fraction of those applications determined where the sponsor could submit a response within 90 days as foreseen in the centralized procedure[117]. For all orphan products a total of 19/43 (44%) and for the selected orphans of

[117] Notice to Applicants, Volume 4A, Chapter 4 Centralized procedure.

7/17 (41%) the response time was below this threshold. Compared to that, in 11/17 (65%) reference products initial answers were submitted within three months (difference not significant: Chi square test P = 0.152 and P = 0.169).

Overall, these data show that the time to submission of the answer of the first list of questions tends to be shorter for non-orphan drugs but these effects are not too pronounced and appear to be superimposed by the general variability of data.

Influence of Protocol Assistance on the Marketing Authorisation

It was furthermore investigated if protocol assistance has a positive effect on the centralized procedure. Again, the time to submission of answer on the first list of questions is used as a surrogate. The mean time (± SD) for products where the sponsor had obtained PA was 80 ± 45 days. In contrast, for projects where no scientific advice at the EMEA was obtained during development the time was with 115 ± 82 days significantly longer (two sided Student t-test P = 0.007). The difference amounts to as much as five weeks.

These data indicate that Protocol Assistance during development of orphan medicinal products might result in an overall smoother authorisation process. For this reason, such procedure is strongly recommended. One confounding variable could be that more experienced regulatory affairs manager tend to apply for PA more often. Their experience should also become obvious from overall success during authorisation. However, this constraint has no implication on the overall conclusion to recommend protocol assistance.

Inspections

The question was investigated if inspections are a particular issue in the authorisation of orphan medicinal product or not. Such suspicion was also based on the experiences with OMPs that received a final negative opinion (see section *Negative Opinion* below). It is striking to notice that two of these have in common that the authorisation request was based on a single main study (Lenalinomide Celgene Europe and Kiacta). In both cases an inspection at the study site was performed and resulted in concerns over the reliability of the study.

For this reason, EPARs of the 18 selected orphan medicinal products and non-orphan products were reviewed for information on inspection during the CHMP/CPMP evaluation. An overview of the results is presented in the table below.

Table 21: Inspection frequency of orphan and non-orphan medicinal products.

	Orphan Medicinal Products	**Reference Products**
Available Data	17	16
Inspections (%)	6 (35%)[118]	4 (25%)
GMP	4	2
GCP	1	1
Unknown	1	1

Inspections appear to be as frequent during evaluation of OMP as of non-orphans (35% versus 25%). The small difference is not significant (P = 0.243, Fischer's exact test). For orphan drugs the majority of the inspections referred to GMP units rather than GCP. This is remarkable as it was outlined above that negative findings during GCP inspections contributed to a negative opinion. However, it cannot be said how many of the inspections

[118] During the evaluation of Tracleer two inspections were performed, one GCP and one GMP.

were carried out on a routine base (i.e. randomly assigned) and how many due to a concrete suspicion. But overall no significant difference is obvious.

Summary

In conclusion, the different parameters analysed do not give any indication that the authorisation process is more critical or on the other hand more benevolent for orphan medicinal products compared to normal drugs. No significant difference was obvious for active review time, number of list of questions or inspection frequency. On the other hand, it was observed that the time to answer to the first list of questions tended to be shorter and the fraction of procedures where the answer was submitted in less than 90 days for non-orphan drugs compared to OMPs. However, this small difference might be due to the severity of the question as well as to the organisation of the sponsor company.

In addition, the reply process to the first list of question was significantly faster for orphan product where protocol assistance was obtained during development. This indicates the high impact of this scientific advice on the data quality. For this reason, such procedure is strongly recommended.

Orphan Condition versus Authorized Indication

It is important to clearly distinguish between the orphan condition (that is defined in the designation process) and the authorized indication. The indication results from clinical development and refers to the patient group for that a favourable risk/benefit has been demonstrated. In most cases the authorized indication is much narrower than the orphan condition. For instance the orphan condition for Revlimid is “Treatment of multiple myeloma” and the authorized indication is “in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy”.

The orphan condition has to cover the authorized indication. This is a prerequisite to enable the sponsor to take advantage of the orphan incentives (after authorisation). In this context the above mentioned strategy to define the orphan condition as broad as possible (which is also supported from the COMP philosophy to avoid subsets wherever possible) can ease the orphan authorisation procedure. This is due to the fact that it may avoid that the authorized indication – as a consequence of the development activities – lies at least in part outside the scope of the orphan condition.

One interesting example is Siklos in the treatment of sickle cell syndrome (SCS): The orphan condition was “treatment of sickle cell syndrome” and the authorized indication is “prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in paediatric and adult patients suffering from symptomatic Sickle Cell Syndrome”. Formally, this is a switch from “treatment” to “prevention”. However, the decision of accepting this change is adequate and in the spirit of the orphan regulation: From a medical point of view both refers to the same: relieving patients suffering from SCS. A curative treatment is difficult to envisage for such disease caused by a gene defect - potentially gene therapy. The aim of treatment is relieving the signs and symptoms of the disease which is achieved as obvious from the therapeutic indication.

The distinction between the orphan condition and the authorized indication is also of importance with regards to the market exclusivity. It has to be kept in mind that this incentive refers to the indication rather than the condition. For this reason, if possible one might aim at an indication that is as broad as possible during development.

Exceptional Circumstances

Marketing authorisation under exceptional circumstances is a special form of authorisation for projects where no comprehensive data on the safety and efficacy can be provided. The legal basis for this procedure is Article 14(8) of Regulation (EC) 726/2004 (30 April 2004), details are defined in the Guideline on Procedures for the Granting of a Marketing Authorisation under Exceptional Circumstances, Pursuant to Article 14(8) of Regulation (EC) No 726/2004 adopted by the CHMP[119].

Products for which the applicant can demonstrate in this application that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- in the present state of scientific knowledge, comprehensive information cannot be provided, or
- it would be contrary to generally accepted principles of medical ethics to collect such information,

may be eligible for marketing authorisation under exceptional circumstances.

Consequently, the authorisation under exceptional circumstances is granted subject to a requirement for the applicant to introduce specific procedures, in particular concerning the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken.

As rarity is explicitly mentioned it is obvious that such procedure might be of relevance for orphan medicinal products. However, it has to be kept in mind that “exceptional circumstances” and “orphan designation” are two independent procedures.

Exceptional Circumstances and Orphan Medicinal Products

A total of 25 products authorized under exceptional circumstances are listed on the EMEA website[120]. Of these, 16 refer to orphan medicinal products and nine to non-orphans. As only 48 orphan medicinal products were authorized at that time it can be concluded that approximately every third orphan medicinal product is authorized under exceptional circumstances (33%). In contrast, only nine marketing authorisations of non-orphan medicinal products were done under exceptional circumstances. During the time period from January 2000 till July 2008 in total 170 of these drugs were authorized resulting in a fraction of 5.3% for authorisations under exceptional circumstances. It can therefore be concluded that it is six-fold more likely that an orphan drug gets authorized under exceptional circumstances than a non-orphan. This difference is highly significant (Fischer’s exact test: $P < 0.0001$).

In all cases for the orphan medicinal products the justification was rarity of the disease which is not surprising as rarity is a *sine qua non* for orphan drugs. Interestingly, for two of these non-orphans (ATRyn and Foscan) rarity was the justification listed in the Public Summary EPAR. Another two of these products are used in the treatment of orphan disease but were not authorized as orphan drugs (Velcade for the treatment of multiple myeloma and MapCampath for the treatment of CLL). Two additional “exceptional non-orphan” products refer to vaccines for influenza H5N1 infection. As there are (luckily) so

[119] EMEA/357981/2005, 15 December 2005.

[120] http://www.emea.europa.eu/htms/human/epar/a.htm

far no cases of bird flu in the Western civilisation clinical development cannot be performed and therefore comprehensive evidences cannot be provided.

All this clearly indicates that rarity is the most important criterion for granting exceptional circumstances. As orphan disease are *per definitionem* rare it will be analysed which criteria should apply in particular for such projects.

An important question is under which circumstances orphan medicinal products could be authorized under exceptional circumstances. Table 22 presents the total number of patients in the EU for those orphan projects that have received marketing authorisation so far[121].

Table 22: Prevalence of orphan conditions with products authorized under exceptional circumstances:[122]

Medicinal Product	Orphan Condition	Prevalence per 10,000
Aldurazyme	Treatment of Mucopolysaccharidosis, type I	< 0.1
Atriance	Treatment of acute lymphoblastic leukaemia	1.1
Elaprase	Treatment of Mucopolysaccharidosis, type II (Hunter Syndrome)	< 0.1
Evoltra	Treatment of acute lymphoblastic leukaemia	0.6
Increlex	Mecasermin	1.1
Naglazyme	Treatment of Mucopolysaccharidosis, type VI (Maroteaux-Lamy Syndrome)	< 0.1
Onsenal	Treatment of Familial Adenomatous Polyposis	< 0.1
Orfadin	Treatment of tyrosinaemia type I	< 0.1
Prialt	Treatment of chronic pain requiring intraspinal analgesia	1.3
Replagal	Treatment of Fabry's disease	< 0.1
Revatio	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	1.1
Trisenox	Treatment of acute promyelocytic leukaemia	0.9
Ventavis	Treatment of primary and of the following forms of secondary pulmonary hypertension: connective tissue disease pulmonary hypertension, drug-induced pulmonary hypertension, portopulmonary hypertension, pulmonary hypertension associated with congenital heart disease, chronic thromboembolic pulmonary hypertension	2.7
Xagrid	Treatment of essential thrombocythaemia	2.8
Yondelis	Treatment of soft tissue sarcoma	0.5
Zavesca	Treatment of Gaucher Disease	0.5

This table demonstrates that "exceptional circumstances" were granted for many products for very rare disease (i.e. prevalence below 1 per 100,000 or less than 5,000 patients in the whole EU). Still there are examples for such diseases that were granted a normal orphan authorisation (Fabrazyme, Carbaglu, Savene and Busilvex). On the other hand,

[121] The number of cases is normalized for a total European population of 490 mio.

[122] Data derived from the individual PSO

products for orphan conditions as high as 2.8/10,000 were authorized under exceptional circumstances.

It is stated in the procedural aspects that "designated orphan products are eligible for approval under exceptional circumstances only if the criteria considered for the approval under exceptional circumstances are fulfilled". However, the data presented above show that orphan products being developed for diseases with a prevalence as high as 2.7 per 10,000 were authorized under exceptional circumstances due to pronounced rarity of the disease.

One potential conclusion could be that for all OMPs for diseases with a prevalence below the threshold of 2.7 per 10,000 is sufficiently rare to apply for authorisation under exceptional circumstances.[123] This is warranted for the majority of orphan drugs. However, still not all OMPs are authorized using this particular procedure. There are several reasons for this. The most important reason is that the orphan condition should not be mixed up with the authorized indication. Most likely the availability of patients in the targeted indication is of more importance than the overall prevalence of the condition. This figure is much smaller than the overall prevalence in most cases.

This conclusion is supported by the fact 37.5% (6/16) of all orphan medicinal products authorized under exceptional circumstances are intended for the treatment of a condition with a prevalence below 0.1 per 10,000 in the general population whereas the fraction is 25.8% (8/31) for "not exceptional" OMPs. The relative difference of 45% observed is not significant (Fischer's exact test, P = 0.18). A particularly interesting example refers to the two orphan products authorized for the treatment of Fabry's disease, Fabrazyme and Replagal. Despite development in the same indication and similar numbers of patients included[124], Replagal is authorized under exceptional circumstances whereas Fabrazyme is not

For this reason, the justification why authorisation under exceptional circumstances is adequate should comprise information why recruitment of sufficient patients was challenging. Of course, an overall prevalence analysis is important part of such reasoning In any case, this approach should be discussed as early as possible with the EMEA and Rapporteur/Corapporteur, respectively.

It is of interest to note that it is nowhere requested formally that a favourable risk/benefit ratio has to be obvious. On the other hand, it can be expected that this is a general prerequisite for authorisation. In fact, the data presented in the previous section indicate that statistical significance for primary endpoints is standard for orphan products as well.

Procedural Aspects

Procedural aspects for marketing authorisations under exceptional circumstances are presented in detail in the Annex of directive 2001/83 as well as in the guideline for authorisation under exceptional circumstances[125].

First of all, the applicant should submit a statement on the appropriateness of the granting of a marketing authorisation under exceptional circumstances in the notification to the EMEA of their intention to submit a marketing authorization application (at least 6 months before submission). Then, if the applicant considers that the grounds for approval under exceptional circumstances should apply, the applicant should tick the box 1.5.2 of the application form and include its justification in module 1, covering the following aspects:

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[123] If the total number in the orphan condition of all patients is compared for products authorized under exceptional circumstances or not a non significant trend for less patients for the "exceptional OMPs" becomes obvious: 34,950 ± 38,820 compared to 53,400 ± 52,000 (Student t-test, P = 0.11).

[124] Whereas in the development for Replagal 41 patients were included into the main studies the respectve number of patients was 58 for Fabrazyme

[125] EMEA/357981/2005

1. A claim that the applicant can show that he is unable to provide comprehensive non-clinical or clinical data on the efficacy and safety under normal conditions of use
2. A listing of the non-clinical or clinical efficacy or safety data that cannot be comprehensively provided
3. Justifications on the grounds for approval under exceptional circumstances
4. Proposals for detailed information on the specific procedures/obligations to be conducted (Safety procedures, programme of studies, prescription or administration conditions, product information).

The proposals for detailed information on the specific procedures/obligations to be conducted shall also be written in accordance with the *Guideline on risk management systems for medicinal products for human use*[126].

The relevant documentation for applications in exceptional circumstances is laid down in Part II of Annex I of Directive 2001/83/EC, as amended. Here it is stated that marketing authorization may be granted on the following conditions:

1. the applicant completes an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile,
2. the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and for a radiopharmaceutical, by an authorized person,
3. the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

If the justification is based on the rarity it should comprise an estimation of the population that might be available for development. This information will be requested for the discussion and evaluation on the development plan and feasibility of studies (including a detailed description of the study design and statistical considerations). In addition, information on the orphan status should be included.

Provisions, Advantages and Disadvantages

Overall the exceptional circumstance procedure offers the opportunity for authorisation despite incomplete clinical data. This is a big advantage for orphan medicinal products where proper development is frequently hampered by the fact that sufficient patients are difficult to recruit.

The authorisation under exceptional circumstances is granted with defined provisions. The applicant will provide an overview of measures and studies to continue or perform after authorisation:

- Safety procedures should be in the form of an EU RMP. The pharmacovigilance plan should describe measures to ensure that MA holder and authority will be informed on any incident relating to the use of the product.
- Detailed list of planned and ongoing studies, including study outline and expected milestones.
- Detailed information on the condition of use (medicinal prescription or potentially request for medicinal supervision during use)
- Proposal how the attention of any consumer might be drawn in the fact of incomplete data in the labelling.

[126] EMEA/CHMP/96268/2005, 14 November 2005

As outlined in the previous section the applicant will be obliged to collect predefined data after granting the marketing authorisation. If the data package is regarded being complete an authorisation under exceptional circumstances might be converted into a normal authorisation. Interestingly, such procedure is not foreseen in the regulatory guidance in contrast to conditional approval which clearly aims at such conversion. MapCampath (alemtuzumab) was authorized under exceptional circumstances for B-cell CLL in July 2001. In 2008 this authorisation was converted into a normal authorisation as the company had supplied the additional information requested. This example demonstrates that such change in the authorisation type is in fact feasible.

A disadvantage for such authorisations is that the risk/benefit ratio is reassessed annually. This requires additional efforts by the sponsor as the authorities have to be informed on the advance in development. The risk for the authorisation holder is of course that it might turn out during further development that the ratio is no longer favourable. But to our information there is no example so far where an authorisation under exceptional circumstances was withdrawn for such reasons.

Examples for Data Awaited

The Summaries of the EPAR always comprise a section on the data that are still expected. An overview is presented in the table below. Interestingly the missing data to a full dossier are termed “awaited data” indicating that the development process is still ongoing which appears more adequate to “conditional approval” where it is expected that sooner or later all information will be available.

Table 23: Awaited data for orphan medicinal products authorized under exceptional circumstances.[127]

Product	Awaited Data
Alduryzyme	Reactions to infusion and formation of antibodies
Atriance	Information from safety studies and young adults including data from combination therapy with other anticancer compounds
Elaprase	Long-term effects and potential formation of antibodies, data in young children and information on potential target organs
Evoltra	Data from paediatric patients and patients with kidney disease; set-up a registry for monitoring side effects
Increlex	Long-term safety study (treatment start in young children)
Onsenal	Additional study to collect more information on safety and efficacy
Orfadin	Post-marketing surveillance to monitor use and safety
Prialt	Data on long-term use of the medicine, in particular induction of tolerance
Replagal	Data on long-term treatment, other dosages, maintenance dosages, studies in children
Revatio	Data on long-term use of the medicine
Trisenox	Data on the use in liver cancer and combination therapy
Ventavis	Data on long-term use of the medicine
Xagrid	Comparison with hydroxyurea; investigation in particular subgroups
Yondelis	Assessment which patients will most likely respond to the treatment; study in myxoid liposarcoma
Zavesca	Information on safety and efficacy, e.g. in particular patient subgroups

[127] Information derived from the summary for the public as part of the EPAR.

Overall the most important data awaited are:

- Induction of tolerance or antibody formation for protein or peptide drugs (in 60% of all products falling into this therapeutic class)
- Additional information with regards to efficacy (including combination therapy, selection of doses, or comparison to other products in 44% of all cases
- Long-term safety and/or efficacy effects (38% of all cases).
- Additional safety information (except for long-term effects and tolerance/antibody induction) in 33%.
- Information on the use of the product in particular subgroups (in particular children) in 31% of all cases presented. It is expected that such issues will decrease in relevance due to the advent of the Paediatric Regulation requiring the development of new drugs in paediatric patients.

It is interesting to note that many of the issues listed above are not directly linked to the rarity of the disease rather than lack of long-term studies which appear not to be necessarily a particular issue for OMPs. In addition, for most of the awaited information it appears to be realistic that the data will be available within the next years raising the question why these products were selected to be authorized under exceptional circumstances rather than to undergo conditional approval. As will be presented below, one possibility is that public health benefit is limited due to the rarity of the disease.[128]

Conditional Approval

General Considerations

Conditional marketing authorisation is defined in the Commission Regulation (EC) No. 507/2006. According to this procedure, products authorized under the centralized procedure may be granted marketing authorisation despite the fact that complete and comprehensive clinical data are not yet available. In such case the following requirements have to be met:

- a positive risk/benefit ratio is obvious from the available data
- it is likely that the outstanding clinical information will be provided
- unmet medical needs will be fulfilled
- the benefits to public health outweigh the risk inherent in the fact that incomplete data are provided.

The sponsor is obliged to pursue a defined development program to complete the information required and to submit the missing data. As soon as safety and efficacy has been reasonably demonstrated this marketing authorisation will be converted in a normal one.

The intention of this procedure is to enable the market entry for drugs that are urgently needed as soon as a reasonable probability exists that this product will be active. In comparison to authorisation under exceptional circumstances in this case it can be expected that a full dossier will be available.

Conditional Approval and Orphan Medicinal Products

A total of six products were granted conditional approval. Of these only two referred to orphan medicinal products (i.e. Diacomit with the active ingredient stiripentol and Sutent but the latter is converted in the meantime to a normal authorisation) and four to non-orphans. As 48 orphan medicinal products were authorized at that time it can be concluded that

[128] Interestingly, despite the fact that there are approximately only 15,000 patients in the EU for the orphan product Diacomit conditional approval was granted.

approximately 4.2% are falling under this particular authorisation procedure. In contrast, four marketing authorisations of non-orphan medicinal products were granted conditional approval. In the same period, 170 of these “normal” drugs were authorized resulting in a fraction of 2.4% for authorisations under exceptional circumstances. The small and not significant difference indicates that conditional approval is of similar relevance for orphan and non-orphan drugs (Fischer’s exact test: P = 0.27). However, this analysis is hampered by the fact that conditional approval that has already been converted into a normal authorisation is difficult to detect. Due to the fact that all OMP EPARs have been reviewed but nor all of non-orphan drugs, it might be that the true fraction for the latter drugs might be underestimated. Accordingly, the difference between both classes of medicinal products could be even smaller.

Overall, marketing authorisations under exceptional circumstances appears more prevalent than conditional approval (in the current status quo there is a fivefold excess). This is worth being noted as the above mentioned guideline states that authorisation under exceptional circumstances should not be granted if conditional approval appears more adequate. One interesting example is MapCampath for the treatment of CLL, a non-orphan drug that was originally authorized under exceptional circumstances. As the company submitted additional information the authorisation was converted into a normal, non-exceptional marketing authorisation. Accordingly, in this example conditional approval would have been more adequate. As outlined in the section on exceptional circumstances the CHMP defines also information that has to be gathered for drugs authorized using this procedure. It appears that despite the principal difference “exceptional circumstances” is used in a similar way as “conditional approval” in particular for treatments of rare diseases.

In conclusion, conditional approval plays no particular role in the authorisation process of orphan medicinal drugs. This is most likely at least in part due to the fact that this procedure is foreseen for cases of public health threats which are much more unlikely for – rare – orphan diseases compared to frequent “normal” diseases.

Well Established Use and Bibliographic Applications

The Orphan Regulation includes the development of established treatments such as cases where old drug might be used in known indications as long as they are not formally authorized in the EU. It is possible to authorize a long-standing and well known treatment that has been off-label used for several years and is well known in the physician community. Such projects benefit strongly from the market exclusivity period as they are typically not protected by patents. For this reason the orphan protection can have a large impact.

In cases of well established use no results of toxicological and pharmacological tests or the results of clinical trials have to be demonstrated (2001/83/EC as amended, Article 10a). To pursue this way the applicant has to demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years. Evidently, an acceptable level of safety and efficacy must be demonstrated on the basis of scientific literature.

Generally, in the development all scenarios exist: applications comprising recent study data as well as literature references as well as applications including only data from the literature or applications exclusively based on own study data – with the latter being most prevalent.

Details on well-established use applications are summarized in Annex I of Directive 2001/83/EC, Part 3 (Toxicological and Pharmacological tests), section I and Part 4 (Clincial Documentation), section I. The time required for establishing a “well established medicinal use” of the component of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community. The application should comprise a full description of the published data

including favourable and unfavourable information. The toxicological/pharmacological documentation should cover all aspects of safety assessment. The clinical documentation should cover all aspects of efficacy evaluation. If information is missing justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking. The expert report must explain the relevance of any data submitted which concern a product different from the one intended for marketing. A judgment must be made whether the product studied can be considered as similar to the product which will be granted a marketing authorisation in spite of the existing difference. Finally, clinical and non-clinical post-marketing experiences with authorized medicinal products containing the same active ingredient are considered being in particular of importance.

Orphan Medicinal Products Authorized According to Article 10a

So far only one orphan medicinal products has been authorized using non-clinical and clinical data derived from literature only. This was Lysodren (mitotane) for the treatment of advanced adrenal cortical carcinoma.

In addition to this examples where Modules 4 and 5 were entirely based on bibliographic information there are also several examples for OMPs that were to a significant proportion based on data published in the scientific literature.

- Cystadane (betain hydrochloride) is authorized under article 8(3) for the adjunctive treatment of homocystinuria. The applications refers in the preclinical and clinical section to literature data as well as own study reports. Efficacy is solely justified on the basis of published information.
- Pedea (ibuprofen injection solution) has been authorized for the treatment of patent ductus arteriosus. Non-clinical data and the majority of clinical data are based on published literature. The former information was for sure easier to collect due to the fact that the active ingredient has been known and used as a drug for decades. Particular clinical studies, such as PK in patients, dose range finder and a main study have been performed by the applicant. Efficacy data were supported by comprehensive information from the literature.
- Siklos (hydroxyurea) for the treatment of sickle cell syndrome (SCS) has been authorized nearly exclusively on the basis of referenced data. However, the product is already on the market for the treatment of oncologic conditions. Efficacy was exclusively demonstrated using published data from scientific literature. Only a PK study has been performed to prove the bioavailability of the newly developed tablets compared to the available capsules and to investigate the PK in SCS patients.[129]

In addition to these examples where the majority of data was derived from the published literature there are other OMPs where some published information was included into the dossier but played a minor role only.

It appears in conclusion that bibliographic data can be of great importance for orphan products. Products on the use of well known compounds (without patent protection) benefit most from the data exclusivity. However, there is only one example of a pure well established use application. This is most likely due to the fact that it is frequently not trivial to derive all information required for a full application from the literature. If those products are also taken into consideration which are mainly (or with regards to efficacy even exclu-

[129] From this example a negative impact of such orphan authorisation becomes obvious: 100 capsules with 500 mg hydroxyurea (HU) cost approximately 170 Euro (Syrea) and 30 film tablets of the new orphan drug containing 1000 mg HU cost nearly 1000 Euro (Siklos). The orphan authorisation has indirectly enabled a fivefold increase in the price (despite a smaller total amount af active substance in packages of the orphan product). Similarly, the ibuprofen injection solution Pedea is available for nearly 500 Euro despite the fact that is contains a cheap generic product. Such examples are the reason that the COMP is reserved towards bibliographic applications.

sively) based of bibliographic data a total of four such projects could be identified, representing as much as 8.3% of all orphan applications.

Marketing Authorisation – Negative Opinion and Withdrawal

Negative Opinions

There are currently seven orphan medicinal products that were refused to be authorized. Seven of these products did not receive initial authorisation and one no extension of indication. Table 24 comprises an overview of the six products that are not authorized in the Community including the reason for the negative opinion by the CHMP or CPMP respectively.[130]

Table 24: Orphan medicinal products that were refused to receive initial marketing authorisation

Product	Active Ingredient	Indication	Reason for Negative Opinion
Ceplene	Histamine dihydrochloride	Maintenance of remission in acute myeloid leukaemia	The single main study did not provide sufficient evidence to allow the approval, because the study's results were not considered to be compelling enough*
Lenalinomide Celgene Europe	Lenalinomide	Treatment of anaemia due to myelodysplastic syndromes	Concerns over the way the main study was carried out (in particular lack of control groups), which meant that the safety was difficult to assess. In addition, following an inspection of the study site there were concerns over the reliability of the study's findings*
Rhucin	Recombinant human C1 inhibitor	Treatment of acute attacks of angioedema in patients with congenital C1 inhibitor activity deficiency	Concerns over the likelihood of the development of antibodies when Rhucin is given more than once, including its impact on safety and effectiveness*
Kiacta	Eprodisate disodium	Treatment of amyloid A amyloidosis	Effectiveness has not been demonstrated sufficiently in the single main study. In addition, following an inspection of the study site there were concerns over the reliability of the study's findings*
Mylotarg	Gemtuzumab ozogamicin	Treatment of acute myeloid leukaemia	No benefit has been demonstrated and significant side effects were observed.
Cerepro	Adenovirus-mediated Herpes simplex virus-thymidine kinase gene	Treatment of patients with operable high-grade glioma	Low number of patients prevented demonstration of any benefit and resulted in insufficient information on the safety.*

[130] Data derived from http://www.emea.europa.eu/htms/human/refusals/background.htm

Mycograb	Efungumab	Treatment of invasive candidiasis in adult patients, in combination with amphotericin B or a lipid formulation of amphotericin B	Quality concerns (e.g. the product may concern high levels of host cell product) and the fact that the size of the safety dataset is too limited to alleviate the concerns related to the quality aspects

* No assessment report available.

In all cases the conclusion was that the benefit of the products did not outweigh the risks and for this reason a negative opinion was adopted.

For one of these medicinal products quality issues triggered the negative opinion (Mycograb, a protein drug). In two additional cases inspection of the study site resulted in concerns of the quality of the data. It is therefore strongly recommended to ensure appropriate quality of data during development (which should be of course a common place during development of drugs![131]). Furthermore, in one projects the small number of patients contributed to refusal of authorisation (Cerepro). In another case, the lack of control groups was an important reason for the negative opinion (Lenalinomide Celgene Europe). This could also be due to the fact that the sponsor only had to cope with the fact that only a limited number of patients was available. However, it appears that such problems could be prevented by means of a prior scientific advice meeting.

Most interestingly the list of drugs for which the CHMP/CPMP recommended to refuse initial marketing authorisation comprises a total of seven OMPs and seven orphan medicinal products. In the time period between January 2000 and July 2008, 48 orphan medicinal products and 170 non-orphan drugs were authorized via the centralized procedure.[132] This means that the CHMP/CPMP adopted for 13% of all OMP applications a negative opinion and for 4% of all non-orphan medicinal products. In conclusion, the risk of not obtaining marketing authorisation is approximately threefold higher for orphan drugs (the difference being significant: Fischer's exact test, P = 0.019).

There are several potential explanations for this observation. Per definition OMPs are used for the therapy of rare disease. If only part of the patients can be treated using this principle the rarity is even more pronounced. For obvious reasons it is more challenging to recruit sufficient patients for proper clinical development. The above mentioned "small population guideline" was adopted in particular to cope with this problem. However, as it is obvious from Table 23 for several of the products that received a final negative opinion the issues appear not to be related to limited number of patients. Here, other factors may also play a role. One potential explanation is that frequently orphan products are developed by small biotech companies that have only a limited product pipeline. This may lead to attempts to get an authorisation of drugs where the data quality is not appropriate as the existence of the company might depend on such project or due to external pressure to get the authorisation in an agreed timeframe. However, in such considerations one should not forget that negative opinions are also observed for non-orphan products.

The Yondelis Case

A negative opinion for Yondelis (trabectedin) was adopted by the CPMP on 24 July 2003. The drug was intended for treatment of patients with advanced soft tissue sarcoma, who had failed anthracyclines and ifosfamide, or had failed ifosfamide and were unsuitable to receive anthracyclines/ifosfamide. The demonstration of efficacy was based on three sin-

[131] Ulrich Granzer: "Do what you got to do but do it proper!"

[132] Data derived from
http://www.emea.europa.eu/htms/human/withdraw/withdrawapp/background.htm

gle-arm studies. Following the scientific assessment procedure, the CHMP concluded that the benefit/risk profile was not favourable. The negative opinion was mainly based on the fact that clinical efficacy had not been adequately demonstrated. In November 2003 an appeal process was finalized and the CPMP confirmed its original opinion.

However, the product was granted marketing authorisation in September 2007. The revised application included data from a randomised phase II study in patients with liposarcoma or leiomyosarcoma. The authorized indication was "*treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients*." Accordingly, the company expanded the data set over a few years before a revised application was submitted successfully.

Initial Negative Opinion – Orphan Drugs versus Non-Orphans

An initial negative opinion was adopted for a total of eight orphan medicinal product applications compared to 46 positive opinions resulting in an initial failure of 17%[133]. Compared to the fact that 11 negative and 137 positive opinions were initially adopted for non-orphan medicinal products – a fraction of 7% – it can be estimated that the chance for success for initial marketing authorisations is significantly worse for orphan medicinal products (Chi square test: P = 0.007). The retrospective analysis indicated that the probability of a positive opinion on the initial application is approximately threefold higher for non-orphan drugs.

Withdrawal of Application or of Marketing Authorisation

Several applications for marketing authorisations of medicinal products have been withdrawn so far. In total, the applications for 22 non-orphan drugs and nine orphan drugs were withdrawn since 2006. In this time 29 orphan drugs and 69 non-orphan products have been authorized resulting in a proportion of 25% and 24%. Accordingly, applications for orphan products are as often withdrawn as those for non-orphans.

To our information no withdrawal of an authorized orphan medicinal product has occurred in the EU so far.

Conclusion

These data clearly indicate that the authorisation of orphan medicinal products compared to non-orphans is significantly more often without success: A positive opinion is less often granted by the CHMP for these products upon initial application and the fraction of a product with final negative decision is much higher compared to "normal" drugs. There are several potential reasons for such negative outcome most important that the low number of patients makes proper development particularly difficult. Strategic considerations might also trigger authorisations requests despite insufficient data for small companies.

In conclusion, independent if an orphan or non-orphan product is developed high quality of data should be ensured.

[133] Differences to the figures mentioned above are due to the fact that these number refer to initial marketing authorisation whereas the latter include also authorisation after appeal or resubmission such as Yondelis

Authorisation in Several Orphan Indications

In general, it is possible to authorize an orphan medicinal product in several orphan conditions. Current examples are presented in Table 25.

Table 25: Examples for orphan medicinal products authorized for more than one condition

Brand Name	Orphan Conditions	No. of Patients[134]	Prevalence[135]
Glivec	CML	34,000	0.7 per 10,000
	ALL	23,000	0.5 per 10,000
	Myelodysplastic diseases	74,000	1.5 per 10,000
	Malignant GIST	2,250	<0.1 per 10,000
	Hypereosinophilic syndrome and chronic eosinophilic leukaemia	46,000	0.9 per 10,000
	Total	**179,250**	**3.6 per 10,000**
Tracleer	PAH	36,000	0.7 per 10,000
	Systemic Sclerosis	50,000	1.0 per 10,000
	Total	**86,000**	**1.7 per 10,000**
Nexavar	HCC	49,500	1.0 per 10,000
	RCC	124,500	2.5 per 10,000
	Total	**174,000**	**3.6 per 10,000**
Sutent	GIST	14,000	0.3 per 10,000
	RCC	124,500	2.5 per 10,000
	Total	**138,500**	**2.8 per 10,000**
Sprycel	CML	44,000	0.9 per 10,000
	AML	99,500	2.0 per 10,000
	Total	**143,500**	**2.9 per 10,000**

There is no formal definition of a threshold for additional extension applications for orphan medicinal products. A frequent interpretation is that the sum of the authorized orphan conditions for the respective product is below 5 per 10,000. This is clearly fulfilled for the examples identified. However, no clear legal basis for such provision was identified. One possibility, to interpret the orphan regulation in such way is if Article 3 laying down the orphan criteria is read in a way that if refers to all orphan conditions and not only one[136].

This threshold is in the spirit of the Orphan Regulation as the procedure for OMPs comprises kind of subvention of the development (e.g. by fee exemption or reduction). This is justified by the interest of patients suffering from orphan diseases to receive adequate treatment and to stimulate the development in this field. As soon as the poor profitability is no longer warranted it appears difficult to justify the incentive any longer. For this reason it is expected that the applicant either resigns the orphan status or alternatively an entirely new authorisation procedure comprising new brand is initiated.

[134] According to Public Summary of Opinions and proportionally adjusted for EU enlargement since initial designation.

[135] Calculated for a population of 498 million (EUROSTAT, 2006)

[136] Such argumentation is not very strong as it is stated in Article 3 (1) a) that an orphan product is "intended for **a** condition …" and not "for conditions".

The example of Revatio/Viagra also demonstrates that an active substance authorized for a non-orphan condition can also be placed on the market for orphan drugs. But in this case a new authorisation with a new drug product, and another brand name were chosen to place the product. For this reason, it is in the regulatory sense the authorisation of a new product rather than an extension of the indication for Viagra.

Similarly, if it is planned to initially place an OMP on the market and initiate afterwards an extension application for non-orphan conditions the same procedure as outlined should apply. Such examples can easily be envisaged in the field of oncology, for example a drug authorized for the treatment of renal cell carcinoma undergoing an extension application for colorectal carcinoma. Such procedure is not formally excluded in the orphan regulation. As the orphan criteria state that the "*medicinal product is intended for […] the treatment [of orphan conditions]*"[137]. However, the regulation does not state that the product is intended ONLY for the treatment of orphan conditions. Nevertheless, the spirit of the orphan regulation and the common reading include the exclusivity for the treatment of the orphan disease. Such request would be handled in a way similar to the above outlined: The COMP would either recommend to resign the orphan status or to file a distinct application.

To our information there has been no example where the orphan status was withdrawn due to issues as outlined.

Summary

In summary, available information indicate that there is no difference with regards to the attitude of the CHMP during the review of applications for marketing authorisation of orphan medicinal products compared to other drugs. This is obvious from the fact that review times, number of list of questions and inspection frequency is similar between both types of drugs.

On the other hand, there are some differences between both types of products obvious during the marketing authorisation process. The reply time to the first list of questions tends to be several weeks longer for OMPs compared to non-orphans. In addition, a negative opinion upon initial request for marketing authorisation is more prevalent for orphan drugs. The same is true for a final negative decision. All these issues could be due to difficulties in the development of orphan medicinal products compared to "normal" drugs as well as to company inherent reasons, such as organisation or strategic implications.

Authorisation under exceptional circumstances is a frequent procedure observed for OMPs. This is at least in part due to the fact that rarity of a disease might qualify for such procedure. This might enable the authorisation despite incomplete data. The disadvantage is that the risk/benefit ratio will be reassessed annually.

In conclusion, an applicant should not expect preferential treatment during the authorisation of an orphan medicinal product. Available data give no indication that the CHMP might be willing to accept significantly impaired data quality to enable market entry for an orphan product. In case major data are missing the applicant is encouraged to contact rapporteur and corapporteur to discuss the possibility of authorisation under exceptional circumstances. For this reason high quality applications should be ensured.

[137] Regulation (EC) 141/2000, Article 3 (1) a).

DISCUSSION

The high number of authorized orphan medicinal products and the more than tenfold higher number of designations clearly demonstrates the high interest and relevance of the pharmaceutical and biotech industry for the development of orphan drugs. In the recent past more than a quarter of all new products authorized under the centralized procedure were orphan medicinal products. The steadily increasing number of orphan designations indicates that the fraction of orphan products might prosper further on. Having in mind the long development timelines and the high attrition rate during drug development the complaint by Joppi and colleagues that the orphan drug development is rising too slowly cannot be supported (2006). The difficulties in development due to low number of patients and severity of disease should also be respected. Increasing the speed in development can be expected to easily sacrifice quality of data. Such consequences should not be supported in particular if it is kept in mind that the probability of an initial negative opinion is significantly higher for orphan products compared to “normal” drugs.

It appears that the introduction of the European Orphan regulation contributed to the positive development of pronounced efforts by pharmaceutical and biotech industry. This is most likely due to the fact that essentially the orphan procedure does not have pronounced disadvantages over all (except for the additional expenses to obtain and maintain the orphan status) and that significant short term (such as reduction of fees) and long term incentives are offered (such as market exclusivity). On the other hand, still most orphan diseases cannot be treated appropriately.[138] For this reason the pronounced medical need continues being high.

As outlined in previous section the most important incentive, the marketing exclusivity is frequently misunderstood: It refers only to the use of identical or similar compounds in the treatment of the same therapeutic indication rather than the orphan condition in general. Despite the fact that there is the request for a new orphan compound to demonstrate significant benefit over the existing treatments this appears to be no major hurdle during marketing authorisation.

Against this background one might think about expanding the scope of the marketing exclusivity to not only identical and similar compounds but all products intended for treatment of the authorized indication of the orphan product. In the event that a new product has a benefit for the affected patients over the available (orphan) treatment it should be authorized independent of the question if it is similar or not. If the product does not offer an additional benefit there is no reason why the marketing exclusivity should be derogated.

CONCLUSION AND OUTLOOK

The European orphan procedure is a highly recognized way for development and authorisation of medicinal products.

Pursuing such approach, due to the rarity of the disease it is strongly recommended to have a global orphan development strategy rather than a pure European process. In fact, depending on the prevalence and competition the sales for orphan drugs can be substantial. For instance the total global sales for Tracleer, an OMP authorized for pulmonary arterial hypertension – one of the more frequent rare diseases with a prevalence in the range of 2.8 per 10,000 – were approximately 750 million Euro in 2006[139].

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[138] One could regard this as a common place as an orphan disease is no longer an orphan disease according to European criteria if it can be treated appropriately.

[139] According to the 2006 Annual Report by Actelion

Such global strategy should in any case include authorisations in the USA as the most important pharmaceutical market. The orphan criteria are stricter in the EU: Prevalence threshold is lower than in the US. In addition, subsets of diseases are not allowed and significant benefit has to be demonstrated which is not requested by the Orphan Drug Act. For this reason, it can be expected that an orphan drug in the EU should also receive designation in the USA but not necessarily vice versa. To support common applications the FDA and the EMEA recently launched a common form for the designation.[140]

Another issue that has to be taken into consideration upon setting up a global strategy for the development of orphan medicinal products is that the prevalence of the disease of interest might differ significantly all over the world. For instance, as already outlined tuberculosis is rare in the European Union but in many countries of the world this disease is a serious thread to public health. Similarly, hepatocellular carcinoma is an orphan condition in Europe but in countries with high prevalence of chronic hepatitis B infection – such as many regions in Africa or Asia – the malignancy is much more frequent.

It is obvious from these examples that even therapies for orphan diseases in the EU can be interesting for development if a global strategy is pursued. In fact, such attractiveness of orphan products will be clearly supported by the incentive provided in Europe.

The fact that more than every fourth product being authorized as an orphan drug clearly highlights the relevance of the European Orphan Regulation. Still, many diseases are neglected. It can be regarded a real issue that there is an estimated total number of 5000 orphan diseases according to the European definition (Joppi et al., 2006). Current orphan diseases comprise only a little more than 30 different conditions. For this reason, there is still a pronounced and urgent need for additional therapies. Simultaneously it is observed that the niche market strategy is pursued by an increasing number of companies, in particular small and medium size enterprises (SME) but also big pharma.[141] Due to the fact that competition during development and after marketing is less pronounced a higher market penetration can be expected in these disease areas compared to the frequently encountered widespread diseases such as hypertension or diabetes.

In conclusion, it is expected that the relevance of orphan products in the overall development of new drugs will even increase in the future.

[140] http://www.emea.europa.eu/htms/human/orphans/guidance.htm

[141] Many SMEs outsource their projects during development to big pharma companies. This contributes indirectly to the involvement of the latter into the development of orphan products.

SUMMARY

The authorisation of orphan medicinal products in the EU is a two-step process. First the project has to receive orphan designation that qualifies for receiving the incentives such as free scientific advice. In a second step the product has to be authorized as an orphan medicinal product.

Initially, the product has to receive orphan designation prior to authorisation. This follows a clearly structured and well defined procedure. The most frequent reason for rejection is invalid definition of the subgroup of a disease. For this reason proper definition of the orphan condition is one of the factors of success for designation. During the designation procedure most issues arise from insufficient demonstration of medical plausibility or justification of a potential benefit for the affected patients.

One of the incentives for orphan products is the possibility to obtain free scientific advice, called protocol assistance for orphan drugs, at the EMEA. This procedure is a critical element of the regulatory strategy and is strongly recommended to pursue in particular as available data indicate that it contributes to a smoother authorisation process in the end.

The development of orphan medicinal products and non-orphan “normal” drugs are distinct with regard to several features. Most important, the number of pivotal studies is much lower for orphans and frequently no comparator group is included. Whereas the former is most likely due to the fact that only few patients are available the latter can be explained by the orphan characteristics. Due to the severity of the disease placebo controls might not be ethical. On the other hand, due to the fact that orphan diseases cannot be treated appropriately there might be no adequate active comparator. In any case the clinical development should aim at statistical significance in the primary endpoint. An underpowered study might be acceptable in case the rarity of the disease can adequately be demonstrated.

Orphan medicinal products are authorized under the centralized procedure. Overall, no difference is obvious in the review process by the CHMP for orphan and non-orphan products. On average, during the authorisation process two lists of questions are issued independent of the product type. Similarly, there is no significant difference of the review time or the overall inspection frequency. Authorisation under exceptional circumstances is a particular way to allow marketing authorisation with incomplete clinical data. One of the potential prerequisites for this procedure is rarity of the indication. For this reason, authorisation under exceptional circumstances is frequently seen for orphan products. However, despite the fact that the legislation states that such a procedure should be used if no complete data package can be expected comprehensive provisions will be defined to ensure that all important missing data will be provided finally.

Retrospectively, it is observed that orphan medicinal products fail significantly more often than non-orphans during the initial marketing authorisation. This can only in part be explained by difficulties in development. Accordingly, irrespective of the question if an orphan product is developed highest data quality should be ensured.

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Commission Regulation (EC) No 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) 726/2004 of the European Parliament and of the Council

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 lying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

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THANK YOU!

ANNEX I – QUESTIONNAIRE ON OMP DESIGNATION

Matthias Dormeyer
Pallenbergstr. 15
50737 Cologne
Germany

matthias.dormeyer@gmx.de

1. BASIS OF THE ORPHAN DESIGNATION

1.1 What was the basis for justification of the orphan disease

- ☐ Prevalence of the condition (B1)
- ☐ Return of investment (B2/C)

1.2 Was the orphan condition already a recognized orphan condition at the time of application for designation?

- ☐ Yes
- ☐ No
- ☐ Unknown/Not applicable/Confidential

1.3 What was the justification for use of the orphan medicinal product in the treatment (prevention, diagnosis) of the orphan condition?

- ☐ No method available (section D1 applicable only)
- ☐ No satisfactory methods available (according to the COMP understanding this means that no medicinal products are authorized for the condition D2)
- ☐ Significant benefit (i.e. authorized medicinal products existed and section D3 is applicable)

1.4 Was the orphan medicinal product authorized in another indication at the time of application for designation?

- ☐ Yes
- ☐ No
- ☐ Unknown/Not applicable/Confidential

1.5 Which data were available at the time of application for orphan designation?

- ☐ In vitro efficacy data
- ☐ Efficacy data from a animal disease model (orphan condition)
- ☐ In vivo toxicology data and or safety pharmacology data
- ☐ Phase I or phase I/II data
- ☐ Phase II data in the orphan condition
- ☐ Phase II data in other conditions
- ☐ Phase III data in the orphan condition

☐ Phase III data in other conditions

☐ Case reports in the orphan condition

☐ Other relevant data (please specify):

☐ Unknown/Not applicable/confidential

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2. DESIGNATION PROCEDURE

2.1 Has a pre-submission meeting been performed before initial submission of the application?

☐ Yes

☐ No

☐ Unknown/Not applicable/confidential

2.2 Have any issues been raised during validation?

☐ Yes

☐ No

☐ Unknown/Not applicable/Confidential

In case yes, with respect to which part of the application?

☐ Orphan Medicinal Product form

☐ Section A1 (Description of the condition)

☐ Section A2 (Proposed therapeutic indication)

☐ Section A3 (Medical Plausibility)

☐ Section A4 (Justification of the life-threatening or debilitating nature of the condition)

☐ Section B1 (Prevalence of the orphan disease or condition in the Community)

☐ Section B2 (Prevalence and incidence of the condition in the Community)

☐ Section B3 (Information on participation in other Community projects)

☐ Section C (Potential for return on investment)

☐ Section D1 (Details of any existing diagnosis, prevention or treatment methods)

☐ Section D2 (Justification as to why methods are not satisfactory)

☐ Section D3 (Justification of significant benefit)

☐ Section E1 (Summary of the development of the product)

☐ Section E2 (Details of current regulatory status and marketing history)

☐ Section F (Bibliography)

☐ Proof of establishment in the EEA

☐ Other (please specify):

In case yes, did you regard the issues raised regard being adequate?

☐ Yes

☐ No: Please specify:

2.3 How many times were validation issues raised by the EMEA?

☐ (no issues at all)

☐ Once

☐ Twice

☐ Three or more times

2.4 Did you receive a list of questions during the evaluation of the application by the COMP?

☐ Yes

☐ No

☐ Unknown/Not applicable/Confidential

In case yes, with respect to which part of the application?

☐ Section A1 (Description of the condition)

☐ Section A2 (Proposed therapeutic indication)

☐ Section A3 (Medical Plausibility)

☐ Section A4 (Justification of the life-threatening or debilitating nature of the condition)

☐ Section B1 (Prevalence of the orphan disease or condition in the Community)

☐ Section B2 (Prevalence and incidence of the condition in the Community)

☐ Section B3 (Information on participation in other Community projects)

☐ Section C (Potential for return on investment)

☐ Section D1 (Details of any existing diagnosis, prevention or treatment methods)

☐ Section D2 (Justification as to why methods are not satisfactory)

☐ Section D3 (Justification of significant benefit)

☐ Section E1 (Summary of the development of the product)

☐ Section E2 (Details of current regulatory status and marketing history)

☐ Section F (Bibliography)

☐ Other (please specify):

2.5 In case a list of questions was raised: Did you travel to the EMEA to answer the questions during a COMP meeting?

- ☐ Yes
- ☐ No
- ☐ Unknown/Not applicable/Confidential

In case yes, did your presentation take place?

- ☐ Yes
- ☐ No
- ☐ Unknown/Not applicable/Confidential

Have other issues been discussed that were not included in the list of questions?

- ☐ Yes
- ☐ No
- ☐ Unknown/Not applicable/Confidential

2.6 Have there been particular discussions with regards to the definition of the orphan condition during the procedure?

- ☐ Yes
- ☐ No
- ☐ Unknown/Not applicable/Confidential

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3. CURRENT STATUS AND FURTHER DEVELOPMENT

3.1 Is the development in the orphan condition still ongoing?

- ☐ Yes
- ☐ No
- ☐ Unknown/Not applicable/Confidential

3.2 Do you intend to request or did you already receive Protocol Assistance?

- ☐ Yes
- ☐ No
- ☐ Unknown/Not applicable/Confidential

In case Protocol assistances was obtained, did you regard the feedback valuable?

- ☐ Yes
- ☐ No
- ☐ Unknown/Not applicable/Confidential

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4. COMMENTS

In case you have additional comments with regards to the orphan medicinal product designation procedure please add below

ANNEX II - AUTHORIZED ORPHAN MEDICINAL PRODUCTS

No.	Brand	Active Ingredient	Orphan Condition	Authorized Condition	EU Number EMEA Number	Authorisation Date	Authorisation Holder	Authorisation Particularities
1.	Replagal	Agalsidase alpha	Treatment of Fabry's disease	For use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease	EU/1/01/189 EMEA/H/C/369	03.08.2001	Shire Human Genetic Therapies AB	-
2.	Fabrazyme	Agalsidase beta	Treatment of Fabry's disease	For use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry Disease	EU/1/01/188 EMEA/H/C/370	03.08.2001	Genzyme Europe B.V.	-
3.	Glivec	Imatinib	Treatment of chronic myeloic leukaemia Treatment of acute lymphoblastic leukaemia Treatment of myelodysplastic diseases Treatment of malignant gastrointestinal tumor Treatment of chronic eosinophilic leukaemia and the hy-	Treatment of: - adult and paediatric patients with newly diagnosed Philadelphia chromosome (bcr-abl) positive (Ph+) chronic myeloid leukaemia (CML) for whom bone marrow transplantation is not considered as the first line of treatment. - adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis. - adult patients with newly	EU/1/01/198 EMEA/H/C/406	07.11.2001	Novartis Europharm Ltd.	-

			pereosinophilic syndrome	diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy. - adult patients with relapsed or refractory Ph+ ALL as monotherapy. - adult patients with myelodysplastic/ myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene rearrangements. - adult patients with advanced hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRα rearrangement. The effect of Glivec on the outcome of bone marrow transplantation has not been determined. - adult patients with Kit (CD 117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST). - adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and/or metastatic DFSP who are not eligible for surgery.				

4.	Trisenox	Arsenic trioxide	Treatment of acute promyelocytic leukaemia	Induction of remission and consolidation in adult patients with relapsed/refactory acute promyelocytic leukaemia (APL), characertised by the presence of the t(15;17) translocation and/or the presence of the Pro-Myelocytic Leukaemia/Retinoic-Acid Receptor-alpha (PML/RAR-alpha) gene. Previous treatment should have included a retinoid and chemotherapy.	EU/1/02/204 EMEA/H/C/388	05.03.2002	Cephalon Europe	Exceptional circumstances
5.	Tracleer	Bosentan	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	(PAH) to improve exercise capacity and symptoms in patients with grade III functional status. Efficacy has been shown in: • Primary (idiopathic and familial) PAH • PAH secondary to scleroderma without significant interstitial pulmonary disease • PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology Tracleer is also indicated to reduce the number of	EU/1/02/220 EMEA/H/C/401	15.05.2002	Actelion Registration Ltd	

				new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.				
6.	Somavert	Pegvisomant	Treatment of acromegaly	Treatment of patients with acromegaly who have had an inadequate response to surgery and/or radiation therapy and in whom an appropriate medical treatment with somatostatin analogues did not normalize IGF-I concentrations or was not tolerated.	EU/1/02/240 EMEA/H/C/409	13.11.2002	Pfizer Ltd.	-
7.	Zavesca	Miglustat	Treatment of Gaucher Disease	Oral treatment of mild to moderate type 1 Gaucher disease. Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable	EU/1/02/238 EMEA/H/C/435	20.11.2001	Actelion Registration Ltd.	Exceptional circumstances
8.	Carbaglu	Carglumic acid	Treatment of N-acetylglutamate synthetase (NAGS) deficiency	Treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency	EU/1/02/246 EMEA/H/C/461	24.01.2003	Orphan Europe S.A.R.L.	-
9.	Aldurazyme	Laronidase	Treatment of Mucopolysaccharidosis, type I	Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis I (MPS I; a [alpha]-L-iduronidase deficiency) to treat the non-neurological manifestations of the disease	EU/1/03/253 EMEA/H/C/477	10/06/2003	Genzyme Europe B.V.	Exceptional circumstances
10.	Busilvex	Busulfan	Conditioning treatment prior to	Busilvex followed by cyclophosphamide (BuCy2) is	EU/1/03/254 EMEA/H/C/472	09.07.2003	Pierre Fabre Médicament	-

			haematopoietic progenitor cell transplantation	indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option. Busilvex followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation in paediatric patients				
11.	Ventavis	Iloprost	Treatment of primary and of the following forms of secondary pulmonary hypertension: connective tissue disease pulmonary hypertension, drug-induced pulmonary hypertension, portopulmonary hypertension, pulmonary hypertension associated with congenital heart disease, chronic thromboembolic pulmonary hyper-	Treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms	EU/1/03/255 EMEA/H/C/474	16.09.2003	Bayer Schering Pharma AG	Exceptional circumstances

			tension					
12.	Onsenal	Celecoxib	Treatment of Familial Adenomatous Polyposis	Onsenal is indicated for the reduction of the number of adenomatous intestinal polyps in familial adenomatous polyposis (FAP), as an adjunct to surgery and further endoscopic surveillance	EU/1/03/259 EMEA/H/C/466	17.10.2003	Pfizer Ltd	Exceptional circumstances
13.	Xagrid	Anagrelide hydrochloride	Treatment of essential thrombocythaemia	Reduction of elevated platelet counts in at risk essential thrombocythaemia patients who are intolerant to their current therapy or whose elevated platelet counts are not reduced to an acceptable level by their current therapy. An at risk essential thrombocythaemia patient is defined by one or more of the following features: >60 years of age, or a platelet count >1000 x 10^9/l, or a history of thrombo-haemorrhagic events	EU/1/04/295 EMEA/H/C/295	16.11.2004	Shire Pharmaceutical Contracts Ltd	Exceptional circumstances
14.	Litak	Cladribine	Treatment of indolent non-Hodgkin´s lymphoma	Treatment of hairy cell leukaemia	EU/1/04/275 EMEA/H/C/504	14.04.2004	Lipomed GmbH	-
15.	Photobarr	Pofimer sodium	Treatment of high-grade dysplasia (HGD) in patients with Barrett's Oesophagus	Ablation of high-grade dysplasia (HGD) in patients with Barrett's Oesophagus	EU/1/04/272 EMEA/H/C/493	25.03.2004	Axcan International Pharma BV	-

16.	Lysodren	Mitotane	Treatment of adrenal cortical carcinoma	Symptomatic treatment of advanced (unresectable, metastatic or relapsed) adrenal cortical carcinoma. The effect of Lysodren on non-functional adrenal cortical carcinoma is not established.	EU/1/04/273 EMEA/H/C/521	24.04.2004	Laboratoire HRA Pharma	-
17.	Pedea	Ibuprofen	Treatment of patent ductus arteriosus	Treatment of a haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age.	EU/1/04/284 EMEA/H/C/549	29.07.2004	Orphan Europe S.A.R.L.	-
18.	Wilzin	Zinc acetate dehydrate	Treatment of Wilson´s disease	Treatment of Wilson's disease	EU/1/04/286 EMEA/H/C/535	13.10.2004	Orphan Europe S.A.R.L.	-
19.	Orfadin	Nitisinone	Treatment of tyrosinaemia type I	Treatment of patients with confirmed diagnosis of hereditary tyrosinemia type 1 (HT-1) in combination with dietary restriction of tyrosine and phenylalanine	EU/1/04/303 EMEA/H/C/555	21.02.2005	Swedish Orphan International AB	Exceptional circumstances
20.	Prialt	Ziconotide	Treatment of chronic pain requiring intraspinal analgesia	Treatment of severe, chronic pain in patients who require intrathecal (IT) analgesia.	EU/1/04/302 EMEA/H/C/551	21.02.2005	Elan Pharma International Ltd	Exceptional circumstances
21.	Xyrem	Sodium oxybate	Treatment of narcolepsy	Treatment of narcolepsy with cataplexy in adult patients.	EU/1/05/312 EMEA/H/C/593	13.10.2005	UCB Pharma Ltd.	-
22.	Revatio	Sildenafil citrate	Treatment of pulmonary arterial hypertension and chronic thromboembolic PAH	Treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown	EU/1/05/318 EMEA/H/C/638	28.10.2005	Pfizer Ltd.	Exceptional circumstances Similarity

				in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease				
23.	Naglazyme	Galsulfase	Treatment of Mucopolysaccharidosis, type VI (Maroteaux-Lamy Syndrome)	Long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis VI (MPS VI; N-acetylgalactosamine 4-sulfatase deficiency; Maroteaux-Lamy syndrome)	EU/1/05/324 EMEA/H/C/640	24.01.2006	BioMarin Europe Ltd.	-
24.	Myozyme	Alpha-glucosidase	Treatment of Glycogen Storage Disease type II (Pompe´s disease)	Long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α-glucosidase deficiency). The benefits of Myozyme in late-onset Pompe disease have not been established	EU/1/06/333 EMEA/H/C/636	29.03.2006	Genzyme Europe B.V.	-
25.	Evoltra	Clofarabine	Treatment of acute lymphoblastic leukaemia	Treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Safety and efficacy have been assessed in studies of patients </= 21 years old at initial diagnosis	EU/1/06/334 EMEA/H/C/613	29.05.2006	Bioenvision Ltd.	Exceptional circumstances

26.	Nexavar	Sorafenib tosylate	Treatment of renal cell carcinoma Treatment of hepatocellular carcinoma	Treatment of hepatocellular carcinoma Treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy	EU/1/06/342 EMEA/H/C/690	19.07.2006	Bayer Healthcare AG	-
27.	Sutent	Sutinib malate	Treatment of malignant gastrointestinal stromal tumours	Treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance. Treatment of advanced and/or metastatic renal cell carcinoma (MRCC).	EU/1/06/347 EMEA/H/C/687	19.07.2006	Pfizer Ltd.	Originally conditional
28.	Savene	Dexrazoxane	Treatment of anthracycline extravasations	Treatment of anthracycline extravasation	EU/1/06/350 EMEA/H/C/682	28.07.2006	TopoTarget A/S	-
29.	Thelin	Sitaxentan sodium	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension	Treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and in pulmonary hypertension associated with connective tissue disease.	EU/1/06/353 EMEA/H/C/679	10.6.2006	Enzysive (UK) Ltd.	-
30.	Exjade	Deferasirox	Treatment of chronic iron overload requiring chelation therapy	Treatment of chronic iron overload due to frequent blood transfusions (>/= 7 ml/kg/month of	EU/1/06/356 EMEA/H/C/670	28.08.2006	Novartis Europharm Ltd.	-

				packed red blood cells) in patients with beta thalassaemia major aged 6 years and older. EXJADE is also indicated for the treatment of chronic iron overload due to blood transfusions when deferoxamine therapy is contra-indicated or inadequate in the following patient groups: -in patients with other anaemias, -in patients aged 2 to 5 years, -in patients with beta thalassaemia major with iron overload due to infrequent blood transfusions (<7 ml/kg/month of packed red blood cells).				
31.	Sprycel	Dasatinib	Treatment of chronic myeloid leukaemia	Treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML) with resistance or intolerance to prior therapy including imatinib mesilate. SPRYCEL is also indicated for the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.	EU/1/06/363 EMEA/H/C/709	20.11.2006	BMS Pharma EEIG	-

32.	Diacomit	Stiripentol	Treatment of severe myoclonic epilepsy in infancy	Indicated for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI, Dravet's syndrome) whose seizures are not adequately controlled with clobazam and valproate	EU/1/06/367 EMEA/H/C/664	04.01.2007	Laboratory Biocodex	Conditional Approval
33.	Elaprase	Idursulfase	Treatment of Mucopolysaccharidosis, type II (Hunter Syndrome)	Long-term treatment of patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).	EU/1/06/365 EMEA/H/C/700	08.01.2007	Shire Human Genetics Therapies	Exceptional circumstances
34.	Inovelon	Rufinamide	Treatment of Lennox Gastaut syndrome	Adjunctive therapy in the treatment of seizures associated with adjunctive therapy in the treatment of seizures associated with Lennox Gastaut syndrome in patients 4 years and older	EU/1/06/378 EMEA/H/C/660	16.01.2007	Eisai Ltd.	-
35.	Cystadane	Betaine anhydrous	Treatment of homocystinuria	Adjunctive treatment of homocystinuria, involving deficiencies or defects in: - cystathionine beta-synthase (CBS), - 5,10-methylene-tetrahydrofolate reductase (MTHFR), - cobalamin cofactor metabolism (cbl).	EU/1/06/379 EMEA/H/C/678	15.02.2007	Orphan Europe SARL	-
36.	Revlimid	Lenalidomide	Treatment of multiple myeloma	In combination with dexamethasone for the treat-	EU/1/07/391 EMEA/H/C/717	14.06.2007	Celgene Europe Ltd	Similarity

				ment of multiple myeloma patients who have received at least one prior therapy				
37.	Soliris	Eculizumab	Treatment of paroxysmal nocturnal haemoglobinuria	Treatment of patients with paroxysmal nocturnal haemoglobinuria (PNH).	EU/1/07/393 EMEA/H/C/791	20.06.2007	Alexion Europe S.A.S.	-
38.	Siklos	Hydroxycarbamide	Treatment of sickle cell syndrome	Prevention of recurrent painful vaso-occlusive crises including acute chest syndrome in paediatric and adult patients suffering from symptomatic Sickle Cell Syndrome	EU/1/07/397 EMEA/H/C/689	29.6.2007	Addmedica S.A.S.	-
39.	Increlex	Mecasermin	Treatment of primary insulin-like growth factor-1 deficiency due to molecular or genetic defects	For the long-term treatment of growth failure in children and adolescents with severe primary insulin-like growth factor 1 deficiency (Primary IGFD).	EU/1/07/402 EMEA/H/C/704	03.08.2007	Tercica Europe Ltd.	Exceptional circumstances
40.	Atriance	Nelarabine	Treatment of acute lymphoblastic leukaemia	Treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.	EU/1/07/403 EMEA/H/C/753	22.08.2007	Glaxo Group Ltd.	Exceptional circumstances
41.	Gliolan	5-aminolevulinic acid hydrochloride	Intra-operative photodynamic diagnosis of residual glioma	Visualisation of malignant tissue during surgery for malignant glioma (WHO grade III and IV).	EU/1/07/413 n.a.	07.09.2007	Medac	-

42.	Yondelis	Trabectedin	Treatment of soft tissue sarcoma	Treatment of patients with advanced soft tissue sarcoma, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. Efficacy data are based mainly on liposarcoma and leiomyosarcoma patients.	EU/1/07/417 EMEA/H/C/773	17.09.2007	Phar Mar S.A.	Exceptional circumstances Similarity
43.	Tasigna	Nilotinib	Treatment of chronic myeloid leukaemia	Treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib. Efficacy data in patients with CML in blast crisis are not available				
44.	Torisel	Temsirolismus	Treatment of renal cell carcinoma	First-line treatment of patients with advanced renal cell carcinoma who have at least three of six prognostic risk factors	EU/1/07/424 EMEA/H/C/799	19.11.2007	Wyeth Europe Ltd.	Similarity
45.	Thalidomide Pharmion	Thalidomide	Treatment of multiple myeloma	Thalidomide Pharmion in combination with melphalan and prednisone as first line treatment of patients with untreated multiple myeloma, aged ≥ 65 years or ineligible for high dose chemotherapy.	EU/1/08/443 n.a.	16.04.2008	Pharmion Ltd.	Similarity
46.	Volibris	Ambrisentan	Treatment of pulmonary arterial hypertension	Treatment of patients with pulmonary arterial hypertension (PAH) classified as	EU/1/08/451 EMEA/H/C/839	21.04.2008	Glaxo Group Limited	Similarity

			and chronic thromboembolic pulmonary hyper-tension	WHO functional class II and III, to improve exercise capacity (see section 5.1). Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.				
47.	Firazyr	Icatibant acetate	Treatment of angioedema	Treatment of hereditary angioedema in adults with C1-esterase-inhibitor defi-ciency	EU/1/08/461 EMEA/H/C/899	11.07.2008	Jerini AG	-
48.	Ceplene	Histamine hydro-chloride	Treatment of acure myeloid leukemia	Maintenance treatment in combination with inter-leukin-2 in adults with acute myeloid leukaemia	n.a.	n.a.	EpiCept GmbH	n.a

ANNEX III – DETAILS ON REFERENCE PRODUCT

Brand	Active Ingredient	Authorized Condition Therapeutic Indication	EU Number EMEA Number	Authorisation Date	Authorisation Holder	Authorisation Particularities
Aclasta	Zoledronic acid	Treatment of osteoporosis in post-menopausal women at increased risk of fracture. Treatment of Paget's disease of the bone.	EU/1/05/308 EMEA/H/C595	15 April 2005	Novartis Europharm Ltd	-
Adenuric	Febuxostat	Treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred (including a history, or presence of, tophus and/or gouty arthritis).	EU/1/08/447 EMEA/H/C/777	21 April 2008	Ipsen Manufacturing Ireland Ltd.	-
Circadin	Melatonin	Circadin is indicated as monotherapy for the short-term treatment of primary insomnia characterized by poor quality of sleep in patients who are aged 55 or over	EU/1/07/392 EMEA/H/C/695	29 June 2007	RAD Neurim Pharmaceuticals EEC Ltd	-
Cyanokit	Hydroxocobalamin	Treatment of known or suspected cyanide poisoning Cyanokit is to be administered together with appropriate decontamination and supportive measures.	EU/1/07/420 EMEA/H/C/806	23 November 2007	Merck Santé S.A.S.	-
Exforge	Amlodipine + valsartan	Treatment of essential hypertension. Exforge is indicated in patients whose blood pressure is not adequately controlled on amlodipine or valsartan monotherapy.	EU/1/06/370 EMEA/H/C/716	17 January 2007	Novartis Europharm Ltd.	-
Extavia	Interferon beta-1b	Extavia is indicated for the treatment of: - Patients with a single demyelinating event with an active inflammatory	EU/1/08/454 EMEA/H/C/933	20 May 2008	Novartis Europharm Ltd.	-

		process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis (see section 5.1 of SPC). - Patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years. - Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.				
Galvus	Vildagliptin	Vildagliptin is indicated in the treatment of type 2 diabetes mellitus: As dual oral therapy in combination with - metformin, in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy with metformin, - a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of a sulphonylurea and for whom metformin is inappropriate due to contraindications or intolerance, - a thiazolidinedione, in patients with insufficient glycaemic control and for whom the use of a thiazolidinedione is appropriate.	EU/1/07/414 EMEA/H/C/771	26 September 2007	Novartis Europharm Ltd.	-
Lyrica	Pregabalin	**Neuropathic Pain** Lyrica is indicated for the treatment of peripheral and central neuropathic pain in adults. **Epilepsy:** Lyrica is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.	EU/1/04/279 EMEA/H/C/546	6 July 2004	Pfizer Limited	-

		Generalised Anxiety Disorder: Lyrica is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.				
Kinzalkomb	Telmisartan + hydrochlorothiazide	Treatment of essential hypertension. Kinzalkomb fixed dose combination (40mg telmisartan/12.5mg hydrochlorothiazide, 80mg telmisartan/12.5mg hydrochlorothiazide) is indicated in patients whose blood pressure is not adequately controlled on telmisartan alone. Kinzalkomb fixed dose combination (80mg telmisartan/25mg hydrochlorothiazide) is indicated in patients whose blood pressure is not adequately controlled on Kinzalkomb (80mg telmisartan/12.5mg hydrochlorothiazide) or patients who have been previously stabilised on telmisartan and hydrochlorothiazide given separately	EU/1/02/214 EMEA/H/C/415	19 April 2002	Bayer Healthcare AG	-
MapCampath	Alemtuzumab	MabCampath is indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia (B-CLL) for whom fludarabine combination chemotherapy is not appropriate.	EU/1/01/193 EMEA/H/C/353	6 July 2001	Genzyme Europe BVs	(Originally exceptional circumstances)
Rasilez	Aliskiren	Treatment of essential hypertension.	EU/1/07/405 EMEA/H/C/780	22 August 2007	Novartis Europharm Ltd.	-
Temodal	Temozolomide	Temodal is indicated for the treatment of patients with: - newly diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment - malignant glioma, such as glioblastoma multiforme or anaplastic astro-	EU/1/98/096 EMEA/H/C/229	20 January 1999	SP Europe	-

		cytoma, showing recurrence or progression after standard therapy				
Tarceva	Erlotinib hydrochloride	Non-small cell lung cancer (NSCLC): Tarceva is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen. When prescribing Tarceva, factors associated with prolonged survival should be taken into account. No survival benefit or other clinically relevant effects of the treatment have been demonstrated in patients with EGFR- negative tumours . Pancreatic cancer: Tarceva in combination with gemcitabine is indicated for the treatment of patients with metastatic pancreatic cancer. When prescribing Tarceva, factors associated with prolonged survival should be taken into account . No survival advantage could be shown for patients with locally advanced disease.	EU/1/05/311 EMEA/H/C/618	19 September 2005	Roche Registration Ltd	-
Tyveb	Lapatinib ditosylate monohydrate	Tyverb, in combination with capecitabine, is indicated for the treatment of patients with advanced or metastatic breast cancer whose tumours overexpress ErbB2 (HER2). Patients should have progressive disease following prior therapy which must include anthracyclines and taxanes and therapy with trastuzumab in the metastatic setting (see section 5.1).	EMEA/H/C/795	10 June 2008	Glaxo Group Ltd.	Conditional approval

Velcade	Bortezomib	VELCADE is indicated as monotherapy for the treatment of progressive multiple myeloma in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.	EU/1/04/274 EMEA/H/C/539	26 April 2004	Janssen Cilag International NV	Exceptional circumstances
Vimpat	Lacosamide	n.a.	n.a	n.a.	UCB Pharma	-
Zevalin	Ibritumo-mab tiuxetan	The [^{90}Y]-radiolabelled Zevalin is indicated as consolidation therapy after remission induction in previously untreated patients with follicular lymphoma. The benefit of Zevalin following rituximab in combination with chemotherapy has not been established. The [[^{90}Y]-radiolabelled Zevalin is indicated for the treatment of adult patients with rituximab relapsed or refractory CD20^{+} follicular B-cell non-Hodgkin's lymphoma (NHL).	EU/1/03/264 EMEA/H/C/547	16 January 2004	Bayer Schering Pharma AG	-
Zonegran	Zonisamide	Zonegran is indicated as adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation.	EU/1/04/307 EMEA/H/C/577	10 March 2005	Eisai Ltd	-

ANNEX IV – SUMMARY MASTER THESIS PETER SATTLER

Assessment of potential similarity between orphan drugs[142]

Dr. Peter Sattler, 2007

The incentives of the European orphan drug regulation attracts companies to invest in new drugs for the treatment of rare diseases. Especially the market exclusivity of 10 years for the originator against similar competitors justifies the high development costs for new orphan drugs. Therefore the term similarity has an important rule within the orphan drug regulation. The legal stipulation of similarity assessment is given in the Regulations (EC) No. 141/2000, 847/2000 and a community EC Draft Guideline from 2004.

The interpretation of this similarity definition by the competent authority can be studied in current 5 precedent decisions of the CHMP for orphan drugs in the same indications. In all cases the CHMP decided that the drugs are non-similar and a rapid market access for the competitors was possible. These decisions were in 4 out of the 5 cases in clear consent with the legal definition of similarity. The differences between the orphan drugs regarding structure and mode of action are in all cases major. But an exception is the example Glivec vs. Sprycel. Sprycel is an important treatment option for CML patients with Glivec resistance. But both drugs have a close relationship regarding the mode of action and structure. The reasons for the CHMP to assess non-similarity is based on the argument that the interconnections between the identical structural features N-phenyl-amide, piperazine ring, pyrimidin ring are different. This CHMP interpretation of structural non-similarity shows that competitors with a close structural relationship can also get market access without the obligation to show first clinical superiority. This is in the case of Sprycel acceptable as the drug offers an important treatment option. But the decision shows also the disadvantage of the actual guideline. The rules of similarity contain too many exceptions and caveats for the similarity decision. Therefore smart copies without an additional use for the patient can also get a fast approval.

In order to protect the interests of the industry and to avoid the erosion of the term market exclusivity an important industry organisation (Emerging Biopharmaceuticals Enterprises - EBE) developed an alternative model to assess similarity. In opposite to the current EC Draft Guideline is the definition of similarity very strict. The intention of this model is to have only new innovative orphan drugs or competitive drugs with shown clinical superiority on the market. A comparison of the EBE proposal with the actual CHMP decisions showed that in most cases also an assessment of non-similarity would be given. But a completely different assessment by the EBE proposal would be given for Glivec vs Sprycel. As both drugs have the same INN substem and same mode of action the clinical superiority for Sprycel has to be shown before an approval can be given. The EBE proposal is a reasonable model which supports also the rapid access of innovative orphan drugs. But the model shows also with the example Glivec vs Sprycel one of its main disadvantages. On the one site it protects innovative drugs against smart copies but it also inhibits on the other site the rapid access of needed drugs.

Based on current experience with the assessment of similarity a review of the EC Draft Guideline is needed. The review discussion shall include all aspects get from the current experience with the guideline. Therefore ideas like the EBE model and for the optimisation of the procedure (stronger focus on the structure, integration of subsets of indications, including of the COMP, decision regarding similarity in an early development stage) should be discussed. Based on this review an assessment procedure should be developed which supports the interests of the patients and industry.

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[142] http://www.dgra.de/studiengang/master_thesis/satter.php

Hiermit erkläre ich an Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.