EUROPEAN COMMISSION
HEALTH AND FOOD SAFETY DIRECTORATE-GENERAL

Health systems and products
Medicinal products – authorisations, European Medicines Agency

PHARM 689

PHARMACEUTICAL COMMITTEE
21 October 2015

Subject: **Revision of the 2003 Communication on orphan medicinal product**

Agenda item 2b

Based on the reflections sent by the Member States (PHARM 684) and the experts at the European Medicines Agency, the European Commission has launched a revision of the 2003 Communication on orphan medicinal products which will be replaced by a notice from the Commission. This notice provides interpretative guidance to applicants of the Regulation (EC) No 141/2000 on orphan medicinal products. It focuses on the interpretation of Article 3, 5 and 7 of the orphan Regulation.

The main changes to the 2003 Communication aim at:
- Facilitating the entry of innovative products with a significant benefit over existing treatments and avoiding delays in the entry of generics;
- Clarifying the definition of "significant benefit";
- Encouraging the development of orphan medicinal products for rare diseases (e.g. Ebola);
- Facilitating the procedure for reassessment of the orphan criteria when authorisation application procedures of two orphan medicinal products are running in parallel;
- Introducing the reassessment of the orphan criteria for a new subset of the condition when a sponsor extends the use of its product after marketing authorisation;
- Avoiding the transfer of orphan designation to ascertain that a sponsor receives only one orphan designation per medicinal product and per condition.

With a view to proceed with the public consultation in November 2015, the Commission would appreciate **receiving your comments on the attached draft notice by email to sante-pharmaceuticals-d5@ec.europa.eu by 20 October 2015**.

Action to be taken:
For discussion

Notice from the Commission on Regulation (EC) n° 141/2000 on orphan medicinal products

Regulation (EC) No 141/2000[1] of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products aims at stimulating medicinal product research in the area of rare diseases. It lays down a Union procedure for the designation of medicinal products as orphan medicinal products and provides incentives for the research, development and placing on the market of designated orphan medicinal products.

In accordance with article 3(2) of the Regulation, the Commission adopted Commission Regulation (EC) No 847/2000[2], of 27 April 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'.

This Notice, which replaces the 2003 Communication (2003/C 178/02) is intended to provide interpretative guidance to applicants of the Orphan Regulation, including the European Medicines Agency, the Member States, the pharmaceutical industry and other interested parties.

It focusses on points in relation to Articles 3 (criteria for designation), 5 (procedure for designation and removal from the register), and 7 (Community marketing authorisation) of the Regulation. It should be read in the context of the current interpretative texts and guidance documents for the Regulation listed in Annex 1.

A. GENERAL

The procedure relating to orphan medicinal products is divided into two separate phases.[3] The first phase covers the designation of the product as an orphan medicinal product. Designation can take place at any stage of the development provided that the sponsor can establish that the criteria are met (Article 3 of Regulation 141/2000). Designation as an orphan medicinal product has no effect on parallel developments by different sponsors. It is a tool to identify candidate products in a transparent way and to make them eligible for financial incentives. Designation for each candidate product will be confirmed by a separate Commission decision and the designated candidate product will be entered in the Community Register for Orphan Medicinal Products (Article 5 of Regulation 141/2000).

The second phase covers the marketing authorisation for the product that has been designated as an orphan medicinal product.

B. CRITERIA FOR DESIGNATION – ARTICLE 3(1)

The requirements to be met in order for a medicinal product to be designated as an orphan medicinal product are laid down in Article 3(1) of Regulation No 141/2000, namely, first, that the medicinal product is intended for the diagnosis, prevention or

[1] O.J. L 18, 22.1.2000, p.1
[2] O.J. L 103, 28.4.2000, p.5
[3] Cf. T-74/08, para. 33.

treatment of a rare condition or that the marketing of the product would not generate sufficient return to cover the investment made and, second, that there exists no satisfactory treatment for the condition in question in the EU or, if such treatment exists, that the medicinal product in question will be of significant benefit to patients affected by that condition.[4]

1. The orphan condition

The Commission guideline ENT 6283/00 (See Annex 1) defines a condition as 'any deviation(s) from the normal structure or function of the body, as manifested by a characteristic set of signs and symptoms (typically a recognised distinct disease or a syndrome)'.

When considering an application for orphan designation, the Committee on Orphan Medicinal Products (COMP) may take into account the available data to adapt the condition under application (for example, because the Committee considers that the designable condition is broader than the one under application). In such cases, the Committee on Orphan Medicinal Products shall issue an opinion for the designation of the condition it considers suitable.

2. Prevalence or no return on investment criteria

(a) Prevalence criterion

With regard to the criteria envisaged for designation of an orphan medicinal product the terms of the Regulation do not distinguish between the concepts of a medicinal product intended for the treatment of a condition and a medicinal product intended for the diagnosis or prevention of a condition (e.g. vaccines).

Prevalence calculation for medicinal products intended for the diagnosis or prevention of a condition

In the case of a medicinal product intended for the diagnosis or prevention of a condition, the population "affected by" the condition may be interpreted in several ways.

If a product for the diagnosis or prevention of a condition is effective, this may result in a decrease in the population actually suffering from the disease or condition to less than five in 10 thousand persons in the European Community. The objective of the Regulation is to provide incentives for the development of orphan medicinal products where such incentives are needed. Therefore, in the case of medicinal products intended for diagnosis or prevention (e.g. vaccines), the Commission considers that the prevalence calculation of those persons affected by the condition shall be based on the population to which such a product is expected to be administered on an annual basis. For example, following successful vaccination campaigns, although the vaccinated population is very large, the prevalence of the condition in question may be very low. The prevalence calculation in these cases shall be based on the population vaccinated on an annual basis.

Prevalence of a condition outside the European Union

Article 3(1)a of the Regulation requires conditions which may be considered as orphan to affect "*not more than five in 10 thousand persons in the Community [European Union]"*.

[4] T-140/12, para. 63.

Since prevalence as described in the Regulation refers only to the number of persons affected within the EU, the prevalence of the disease or condition outside the EU has no influence on the interpretation of these criteria. As some communicable diseases may be transmitted from third countries to the European Union (e.g. Ebola, avian influenza), a medicinal product intended to treat a condition which affects a large number of people in certain third countries but which has a low prevalence or a prevalence equal to zero in the EU, is therefore eligible for designation as an orphan medicinal product with respect to the prevalence criterion, and if all other criteria are met, eligible for the benefits set out in the Regulation.

(b) Potential return for investment criterion

Medicinal products intended for a life-threatening, seriously debilitating or serious and chronic condition are eligible for orphan designation even when the prevalence is higher than five per 10 thousands, supposed that the marketing of the product in question is unlikely to generate sufficient return for investment.

An assessment will be based on all costs (past and future development costs) and expected revenues.

3. Intention to diagnose, prevent or treat (Medical Plausibility)

In order to support the rationale for the development of the product in the proposed condition preclinical and/or preliminary clinical data are generally required.

In applications where the proposed orphan indication refers to a subset of a particular condition, a justification for restricting the use of the medicinal product would be needed. Patients in the subset should present distinct and unique evaluable characteristic(s) with a plausible link to the condition and such characteristics would have to be essential for the medicinal product to carry out its action. In particular, the pathophysiological characteristics associated with this subset 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 suffering from the condition. Sub-setting a condition with the use of biomarkers (e.g. personalised medicine) will not be acceptable unless it is proved that the product is ineffective in the rest of the population.

4. Satisfactory method authorised in the Union

Article 3(1)(b) states that the sponsor has to establish "*that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community [European Union]"*. In order to ensure consistency of application and to aid applicants in providing appropriate justification, it is considered important to clarify the notion of "satisfactory" method. In this context, Commission Regulation (EC) 847/2000 asks the applicant to provide details of the "*existing methods, which may include authorised medicinal products, medical devices or other methods of diagnosis, prevention or treatment which are used in the Community [European Union]*."

A marketing authorisation is granted if the risk/benefit assessment is positive. Therefore, at the time of the grant of a marketing authorisation in accordance with EU legislation, the authorised medicinal product is considered to be a satisfactory method as referred to in Article 3(1)b. This being the case, applicants for orphan designation should seek to

show an assumption of significant benefit over any existing authorised medicinal product in accordance with the second part of paragraph Article 3(1)(b), rather than seeking to show that an existing authorised medicinal product is not a satisfactory method.

Authorised medicinal products for the symptomatic treatment of the orphan condition should be included in 'satisfactory treatments' if supported by the Summary of Product Characteristics of the product (refer to section 4.1 of the SmPC).

In this context, a medicinal product authorised in one Member State of the EU is generally deemed to fulfil the criteria of "*authorised in the Community [European Union]"*. It is not necessary for the product to have either a Union authorisation or for it to be authorised in all Member States for it to be considered as "*authorised in the Community [European Union]*".

Any reference to an already authorised medicinal product can only refer to the terms of the marketing authorisation. Therefore the off-label use of an authorised medicinal product [i.e. use not in accordance with the approved Summary of Product Characteristics of the product] cannot be considered as a satisfactory method for the purposes of Article 3(1)(b).

Commonly used methods of diagnosis, prevention or treatment that are not subject to marketing authorisation (e.g. surgery, radiotherapy, medical devices) may be considered satisfactory methods if there is scientific evidence as to the value of such method(s). The scientific evidence would refer to scientific and medical literature or any other relevant information e.g. clinical guidelines by European medical societies.

5. Significant benefit

In accordance with Article 3(1)(b) a medicinal product may be designated as an orphan product even if a treatment exists for the condition in question, provided that it represents a significant benefit to those affected by the condition. Establishing significant benefit takes place in the context of a comparison with an existing authorised medicinal product or method and cannot be limited to an assessment of the intrinsic qualities of the product in question without comparing them with the intrinsic qualities of the authorised methods.[5]

Significant benefit is defined in Commission Regulation (EC) 847/2000 as "*a clinically relevant advantage or a major contribution to patient care.*"

It is apparent from Article 3(1)(b) of Regulation No 141/2000 and the spirit underlying the system established by that regulation that the criteria for a finding of a significant benefit are strict.[6] The purpose of the legislation is to encourage and reward innovative treatments. It implies an investment in research and development of the potential improved medicinal product that can bring meaningful advantages for the patients.[7]

For example, "*a clinically relevant advantage*" may be considered based on :

[5] T-74/08, paragraph 46.
[6] T-140/12, para. 65.
[7] T-264/07, para. 94.

- An improved efficacy for the entire population suffering from the condition, for a particular population sub-set or for a sub-set of the population which is resistant to the existing treatments. The claim should be based on clinical experience;

- A better safety profile or a better tolerability for the entire population suffering from the condition or a particular population sub-set. The claim should be based on clinical experience;

For example, "*a major contribution to patient care*" may be considered based on:

– Ease of self-administration e.g. if the new treatment allows ambulatory treatment instead of treatment in hospital only;

– Important improvement in compliance by changing the pharmaceutical form (e.g. Modified released formulation) only if there are documented difficulties with the existing form and if there are data showing better clinical outcome with the new form;

Significant benefit should not be considered based on:

- A possible increased supply due to shortages of existing authorised products or due to a national marketing authorisation in one or a limited number of Member States;

- Enhancement of the pharmaceutical quality of a product in compliance with the relevant Committee on Medicinal Products for Human Use (CHMP) guidelines which is a part of the obligation of every marketing authorisation holder;

- An alternative mechanism of action per se, to be sufficient for the assumption of significant benefit it needs to be translated into a clinically relevant advantage or a major contribution to patient care.

The applicant is required to establish significant benefit compared with an existing authorised medicinal product or method at the time of designation. As there may be little clinical experience with the orphan medicinal product in question, the justification for significant benefit is likely to be made on assumptions of benefit by the applicant, at the time of designation. In all cases the Committee on Orphan Medicinal Products is required to assess whether or not these assumptions are supported by available data supplied by the applicant.

Protocol Assistance is highly recommended to ensure an appropriate clinical development of the orphan medicinal product. Protocol assistance can also include guidance to demonstrate significant benefit over authorised medicines.

6. Maintenance of orphan designation at the time of marketing authorisation

The criteria laid down in Article 3(1) must continue to be met when the medicinal product designated as an orphan product is granted marketing authorisation as an orphan medicinal product since, pursuant to Article 5(12) of the regulation, a medicinal product which, before marketing authorisation is granted, fails to meet the criteria laid down in Article 3(1) of the regulation, must be removed from the register.[8].

At this stage of the development, companies will typically have more robust data than at the time of designation. The assessment by the Committee on Orphan Medicinal

[8] T-140/12, para. 66.

Products regarding the maintenance of the orphan designation will be based on these data.

The significant benefit should consider a quantitative element that allows the Committee on Orphan Medicinal Products to measure the magnitude of the effect based on direct or when not possible indirect comparative clinical trials with an already authorised medicinal product. The sponsor is expected to comply with established guidelines on development of products in the different indications and to take into account the current medical knowledge to establish the best comparative alternative in each case, when applicable. Any advantage of the designated orphan medicinal product will be considered in the context of experience with authorised products in the orphan condition even if comparative clinical studies are not always possible. In exceptional cases, if it is not possible to generate a sample size big enough to provide statistically comparative evidence or due to the heterogeneous patients' population, it would be possible to adapt clinical trials designs and alternative methods (such as indirect comparative data, historical data).

Where protocol assistance for the justification of significant benefit has been received, the review will assess compliance to the advice given.

Granting an orphan marketing authorisation for a new pharmaceutical form (X) of an existing medicinal product (Y) would prevent the entry of generics of this existing authorised medicinal product (Y) on grounds that such generics would be considered similar to the orphan medicinal product (X). Consequently, the major contribution to patients care of the new pharmaceutical form (X) should be justified in all cases with relevant data showing meaningful benefits for the patients as mentioned above.

In the field of unmet medical need, it may be appropriate to allow medicinal products to go early on the market on the basis of less complete package of data. In such cases, applicants may seek a conditional marketing authorisation. Nevertheless, the limited package of data may not be sufficient to confirm the significant benefit and the orphan designation may be lost. Before considering a conditional marketing authorisation for an orphan medicinal product it is therefore highly recommended to seek protocol assistance. The European Medicines Agency should ensure consistency between the confirmation of the 'unmet medical need' for the conditional marketing authorization and the 'significant benefit' of the purpose of the orphan designation.

C. PROCEDURE FOR DESIGNATION AND REMOVAL FROM THE REGISTER – ARTICLE 5

Article 5 defines the procedure for designation and removal from the register.

In accordance with Article 5(12)b of the Regulation a designated orphan medicinal product is removed from the Community Register of Orphan Medicinal Products "*if it is established before the market authorisation is granted that the criteria laid down in Article 3 are no longer met in respect of the medicinal product concerned*".

This implies that a removal on this basis must be preceded by a reevaluation by the Committee on Orphan Medicinal Products of the criteria laid down in Article 3. Removal in these circumstances might occur if there is evidence that the basis on which the original designation was granted has changed, for example if:

- the assumption of clinical relevant advantage or major contribution to patient care is not supported by data at the time of marketing authorisation;

- the prevalence has increased between the time of the designation and the time of the marketing authorisation following new literature data.

1. Justification of continued fulfilment of the criteria by the applicant

When a sponsor submits an application for marketing authorisation for a designated orphan medicinal product he/she shall include the information that the product concerned has been designated as an orphan medicinal product. In addition the sponsor is requested to submit a report on the criteria that led to the designation of the product as an orphan medicinal product and updated information on the current fulfilment of these criteria.

The information will be assessed in parallel to the marketing authorisation assessment.

In case of reasonable doubt as to whether the criteria for designation continue to be met, the sponsor may be invited to provide additional justification either orally or in writing.

2. Removal from the register

The responsibility for assessing the criteria for orphan designation rests solely with the Committee on Orphan Medicinal Products. The Committee on Orphan Medicinal Products is responsible for giving a scientific opinion on initial designation. As initial designation leads to the inclusion of a medicinal product in the Community Register of Orphan Medicinal Products, it follows that, unless it is at the request of the sponsor, removal from the register must follow the same procedure of scientific opinion followed by a legal decision by the Commission in accordance with Article 5(8).

For the orphan medicinal products approved under the conditional marketing authorisation, further data will be generated post authorisation as part of the specific obligations and are reviewed on an annual basis in the context of the review of the benefit risk balance by the Committee for human medicinal products. In the light of the updated data at the end of the fifth year as provided in Article 8.2 of Regulation 141/2000, a Member State may inform that the criterion on the basis of which market exclusivity was granted may not be met and the agency shall then initiative the procedure laid down in Article 5.

3. Reevaluation of orphan designation criteria at time of Marketing authorisation – preauthorisation phase

The Commission considers that the most appropriate time to reconsider designation is when the marketing authorisation of a designated orphan medicinal product is imminent, that is at around the time of an expected positive opinion from the Committee for Medicinal Product for Human use (CHMP).

When two procedures for granting marketing authorisations for the same condition are running in parallel in the European Medicines Agency, it may be difficult for the second product to show significant benefit over the firstly authorised product. If the two applications are validated and assessed by the CHMP at the same time, the sponsor for the second product should not be required to show significant benefit over the first product.

On the other hand, when the procedures for the simultaneous marketing authorisation applications do not remain in parallel and the positive opinion for the second product compared to the first product is delivered by the CHMP with a difference in time of two CHMP meetings or more, the second sponsor should show data supporting the significant benefit over the first product.

4 Effect of removal from the Community register on marketing authorisation procedure

If a designated medicinal product is removed from the register after the procedure for authorisation in accordance with Regulation (EC) No 726/2004 of the European Parliament and of the Council laying down Community procedures has commenced, it may still be granted a Union marketing authorisation in accordance with that Regulation. However the medicinal product will not be entitled to the subsequent benefits provided for by the Orphan Regulation (e.g. market exclusivity and future fee reductions). On the other hand, none of the benefits enjoyed prior to the removal from the register, such as fee reductions, and which accrued prior to its removal shall be recovered.

5 Transfer of designation to another sponsor

Article 5 (1) of the Regulation lays down that *"In order to obtain the designation of a medicinal product as an orphan medicinal product, the sponsor shall submit an application to the Agency at any stage in the development of the medicinal product before the application for marketing authorisation is made."*

Article 5 (11) of the Regulation stipulates that an orphan designation can be transferred to another sponsor.

Based on a combined reading of those two provisions, the Commission considers that a sponsor can only receive one orphan designation per medicinal product and per condition. New subsequent formulations, route of administrations of the orphan medicinal product already authorised fall within the scope of the existing orphan designation and cannot be rewarded with any additional period of market exclusivity. Moreover, it is not possible to transfer an orphan designation to an applicant who has already a marketing authorisation for the same medicinal product and condition. Any additional pharmaceutical forms should be granted by varying the existing marketing authorisation. In case an applicant asks the European Commission for a separate marketing authorisation for providing a distinction between two pharmaceutical forms and avoid medication errors, this separate marketing authorisation will be subject to the same market exclusivity period. The market exclusivity will be calculated from the date of the first marketing authorisation.

D. UNION MARKETING AUTHORISATION – ARTICLE 7(3)

1. Designated condition vs. authorised indication

Article 7.3 of the Regulation states that *"the marketing authorisation granted for an orphan medicinal product shall cover only those therapeutic indications which fulfil the criteria set out in Article 3"*.

There have been questions regarding the possibility of having a therapeutic indication authorised in the framework of the marketing authorisation procedure, which is different

from the condition that has been accepted in the designation procedure. The Commission considers that if orphan designation and its continuing benefits are to be maintained both the therapeutic indication applied for and the therapeutic indication finally authorised are required to fall within the scope of the designated orphan condition. In order to ensure this the sponsor may request to amend the designation decision, prior to the submission of the MA application or during the process of assessment. If the amended designation is not accepted by Committee on Orphan Medicinal Products or if the applicant does not apply to amend the designation, the authorised indication will not be a designated 'orphan indication' and the product will not benefit from market exclusivity as foreseen in Article 8.

In cases in which the therapeutic indication approved through the marketing authorisation procedure is a subset of the designated orphan condition, the marketing authorisation holder will benefit from market exclusivity for this product, for this indication.

If the same sponsor varies subsequently the marketing authorisation to extend the use of its product for a second subset of the designated orphan condition, the product will not benefit from any additional period of market exclusivity, for that second authorised indication, i.e. the second authorised indication will be covered by the market exclusivity granted on initial authorisation.

It is not uncommon that 'significant benefit' is not established in a broad sense covering all potential uses within an orphan condition, but instead limited to certain subsets in terms of patients or indications. For example, it may be the case that the significant benefit at the initial marketing authorisation stage is limited to second line treatment. In those circumstances the initial marketing authorisation for the orphan medicinal product will be limited to such a therapeutic indication as second line treatment. However, once approved the marketing authorisation holder may wish to extend the use of the product to further therapeutic indications within the same orphan condition or to vary the indication as a first line treatment based on new evidence. While such extensions of the initial marketing authorisation are encouraged for the benefit of patients, the Commission considers that the marketing authorisation holder should be allowed to do so only after a formal verification whether the product for those further therapeutic indications is of significant benefit compared to existing treatments. This will align the requirements for the marketing authorisation holder, who will enjoy the benefits of the orphan regulation, especially in terms of market exclusivity, for an extended marketing authorisation, with those required set under the orphan Regulation for another applicant seeking authorisation for a different subset within the same orphan condition or a first line treatment from the onset.

Consequently, if a sponsor varies its marketing authorisation to a new subset of the condition, the variation will entail a review of the orphan criteria to ascertain that the orphan marketing authorisation complies with Article 7.3. It is important that the Committee on Orphan Medicinal Products checks whether these new therapeutic indications have a significant benefit over existing treatments and that the applicant therefore merits its status of orphan for another sub-set of the condition. If that is not the case, the applicant would have to seek a separate marketing authorisation outside the scope of the orphan legislation.

If a different sponsor applies for a marketing authorisation for a second subset of the designated orphan condition, a new 10-year period of market exclusivity can be obtained for that second product, for that second authorised indication.

If it is considered that the second product (from a different sponsor) is similar to the one that is already authorised and that it is intended for the same therapeutic indication ie the same subset of the designated condition, the application cannot be accepted (Article 8(1)), unless any of the derogations set out in Article 8(3) apply. The designation as an orphan medicinal product and the grant of a marketing authorisation are subject to different criteria and procedures. Therefore, different decisions may be taken relating to, for example, the designated condition and the authorised therapeutic indication. When evaluating an application for designation, the Committee on Orphan Medicinal Products will consider an orphan condition in broad terms in order to avoid designations related to artificial subsets of a particular condition.

If a sponsor subsequently varies the marketing authorisation to include another, separate, designated orphan condition, then a second 10 year period of market exclusivity starting on the date of approval of the variation shall apply to the second orphan indication. The second period of exclusivity shall run in parallel to the first, while maintaining different start and finish dates.

2. Separate marketing authorisation

Article 7(3) provides for the possibility that a sponsor of an orphan medicinal product can *"apply for a separate marketing authorisation for other indications outside the scope of this Regulation"*. On the other hand it is also possible that a marketing authorisation holder of a non-orphan medicinal product may develop the product in a designated orphan condition and obtain orphan designation for this new indication. In both cases Article 7(3) requires that marketing authorisations for orphan medicinal products are handled separately from marketing authorisations for non-orphan medicinal products in order to provide legal certainty that the benefits of market exclusivity provided by the Regulation can be enforced.

E. MARKET EXCLUSIVITY – ARTICLE 8

Comment: It is proposed to remove the interpretation of Article 8 from this notice. The interpretation of Article 8 is already provided in the Commission guidelines C(2008)4077 and 2008/C 242/07. Moreover, all orphan medicinal products have to be authorised through the centralised procedure and no orphan medicinal product can be authorised by the Member States. Consequently, this section from the 2003 Communication is obsolete.

Annex 1

1- ENTR/6283/00 *Revision 4*

Guideline on the Format and Content of Applications for designation as Orphan Medicinal Products (October 2002) and Annex Brussels, 27.03.2014

2- (C2008)4077

Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity

3- 2008/C242/07

Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000 of the European Parliament and of the Council: Review of the period of market exclusivity of orphan medicinal products

2- COMP/436/01 *Final*

Points to Consider on the Calculation and Reporting of the Prevalence of a Condition for Orphan Designation (COMP Adopted March 2002)

3- EMEA/14222/00

Procedures for Orphan Medicinal Product Designation - General Principles *Revision 2 (25/10/02)*

4- EMEA/4795/00

General Information for Sponsors of Orphan Medicinal Products *Revision 1 (25/10/02)*

5- COMP/50/01

Appeal Procedure for Orphan Product Designation

6- COMP/189/01*Final*

Note for Guidance on the Format and Content of the Annual Report on the State of Development of an Orphan Medicinal Product, (Adopted by COMP April 2002)

7- EMEA/H/238/02

EMEA Guidance for Companies requesting Protocol Assistance regarding Scientific Issues

8. Recommendations on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation 2 March 2010, EMA/COMP/15893/2009

All of these documents are available on the European Commission website of DG Health and Food safety and the EMA website.