



Brussels, 27 September 2013

Dear Sir/Madam,

Shire welcomes the opportunity to submit comments as part of the European Commission public consultation on the 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.

Shire supports the overarching goal of the guideline and we offer the following section-specific comments for consideration and clarification by the European Commission.

We look forward to a collaborative dialogue raised in this draft guideline.

If you have any questions, please do not hesitate to contact us at your convenience.

Yours sincerely,

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European Commission Public Consultation: 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		
European Commission Proposed Text	(Page Number / Section)	Shire Comments
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		
<p>1. Name of the active substance The active substance should be declared by its recommended International Non-proprietary Name (INN), accompanied by its salt or hydrate form if relevant. If the ‘recommended’ INN is not available the ‘proposed’ INN should be provided. If no INN exists, the European Pharmacopoeia name should be used or if the substance is not in the pharmacopoeia, the usual common name should be used. In the absence of a common name, the exact scientific designation should be given. Company or laboratory codes are not to be used. Substances not having an exact scientific designation should be described by a statement of how and from what they were prepared, supplemented where appropriate by any relevant details. Where the active ingredient is of herbal origin, the declaration of the active substance should be in accordance with the Note for Guidance on Quality of Herbal Medicinal Products.</p>	<p>Page 5 Information to be included in the application form (Annex):</p>	<p>No additional text or change was included in this section. Shire seeks from the EC more clarity on the level of details expected by the COMP for substances which do not have an exact scientific designation, and where the active ingredient is of biological origin (e.g. details on the cell line used, expression system used).</p>

<p>3. Medical Plausibility</p> <p>It is important to include, as far as possible, a discussion of the results of pre-clinical studies with the specific product, as applied for in the specific condition, or a discussion on preliminary clinical data in patients affected by the condition. All available studies should be submitted at the time of the application.</p>	<p>A. Page 7 Description of the condition</p>	<p>Many sponsors will apply for orphan designation at an early stage in development when it is not possible to provide much product-specific information from pre-clinical studies. This is even more challenging with preliminary clinical data.</p> <p>Therefore, to keep the possibility for sponsors to apply for an orphan designation at any stage of the development, Shire proposes to add to this section similar wording to the one included in the “Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation”.</p> <p>Shire proposes allowing the use of data from other products developed for the same condition with adequate extrapolation and appropriate scientific rationale in the case of a very early stage designation (e.. “Since in many cases, at the time of designation, little or no clinical experience is available, it is important that the relevance of in vitro and in vivo preclinical models presented in the application is discussed in the context of the condition and when appropriate reference should be made to other products developed for the same condition”).</p>
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<p>Special considerations</p>	<p>Page 8 B. Description of the condition</p>	<p>Compared to the previous version of the guideline, Shire notes that the case (c) was removed from the guideline:</p> <p>(c)Exceptionally, the need for a particular treatment modality (regardless of underlying diseases) can be considered as a valid criterion to define a distinct condition.</p> <p>Shire proposes to the EC to consider keeping this specific case in the revised guideline as this special consideration seems to be relevant for some specific orphan conditions.</p>
<p>1. Prevalence and incidence of the condition in the Union</p> <p>Where designation according to Article 3(1) (a) paragraph 2, is sought, information on the prevalence and incidence in the Union of the condition at the time at which the application for designation is made should be provided for information purposes.</p>	<p>Page 10 B. Prevalence of the condition</p>	<p>A definition is provided for the prevalence in the first paragraph below section B.</p> <p>Shire seeks additional clarity by proposing to the EC to include a definition of an incidence in this section.</p>
<p>2. Justification as to why methods are not satisfactory</p> <p>The sponsor should provide justification as to why the methods reviewed are not considered satisfactory. This may be based on either clinical information or on scientific literature. It should be noted that, where medicinal products authorized in the proposed orphan indication exist they would be viewed as “satisfactory methods” and the sponsor would be required to argue “significant benefit”.</p>	<p>Page 12 D. Other methods for diagnosis, prevention or treatment of the condition.</p>	<p>In order to clarify the EMA/COMP position that commonly used methods of diagnosis, prevention, or treatment that are not medicinal products may be considered “satisfactory methods,” Shire suggests adding the text in italics to the end of this paragraph:</p> <p>The sponsor should provide justification as to why the methods reviewed are not considered satisfactory. This may be based on either clinical information or on scientific literature.</p>

		<p>It should be noted that, where medicinal products authorized in the proposed orphan indication exist they would be viewed as “satisfactory methods” and the sponsor would be required to argue “significant benefit”. <i>Furthermore, if there is expert consensus on the value of commonly used methods of diagnosis, prevention, or treatment of the proposed orphan indication, where such methods are not subject to marketing authorisation, these methods could be considered “satisfactory methods” and the sponsor would be required to argue “significant benefit”.</i></p>
<p>3. Justification of significant benefit</p> <p>“Justifications provided by the sponsor on the potential increase in supply/availability have to be discussed with regards to whether these could be translated into a clinically relevant potential significant benefit for the patient population in all Member States.”</p>	<p>Page 13 D. Other methods for diagnosis, prevention or treatment of the condition</p>	<p>Shire proposes to the EC to provide additional examples in the guideline of what is expected from COMP regarding criteria to provide to justify “clinically relevant potential significant benefit for the patient population”.</p> <p>Moreover, significant benefit based on an assumption of a major contribution to patients have mainly been based on two criteria: more convenient routes of administration improving patient compliance or an improved availability of the product for the patient population.</p> <p>Indeed it would be useful as for the recommendation document to also add a paragraph related to improvement of treatment compliance.</p>

		<p>In addition, justification of significant benefit at the time of registration for OMP with conditional approval might be challenging as no additional data can be submitted after marketing authorisation to support significant benefit. A more detailed definition and structure of the scientific justifications for significant benefit, including a review of the level and type of data requirements, particularly regarding secondary endpoints in relation to major contribution to patient care, and different comparators would be useful to the sponsor.</p>
<p>H. CHANGE OF AN EXISTING DESIGNATION Change of an existing designation for an orphan medicine is possible as foreseen in the Commission Communication (C178/2 of 2003). During the development of the product, the condition may need to be modified if it is scientifically justified, such as when there is a change in the classification of a disease or the name of the condition is modified. The sponsor should send a revised application form and revised sections A-E. In sections A-E the sponsor should define and justify the change of the condition and update any relevant sections accordingly e.g. prevalence. The sponsor should specify the reference to the existing designation under section I.1.3.</p>	<p>Page 15 H. Change of an existing designation</p>	<p>Shire welcomes the EC willingness to have the possibility to change an existing designation if additional scientific information becomes available and impacts the information included in the orphan designation. However Shire proposes to the EC that this section be expanded with more information regarding implementation of approved changes which may apply to similar orphan products or orphan products designated in the same condition (e.g. up to the sponsor to make the change or request made by the COMP to re-evaluate the designation for all designated products concerned by the change.)</p>