27 September 2013

Submission of comments on Revision 4 of the Guideline on the format and content of application for designation as orphan medicinal and on its transfer from one sponsor to another (ENTR/6283/00 Rev 4) and Revised Application form for orphan medicinal product designation

Comments from:

Name of organisation or individual
EBE / EuropaBio Contact: Piers Allin (piers@ebe-biopharma.org)

1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
	Currently, a common EMA-FDA application form exists, which can be used in both regions. However, the full application content and requirements are still different between the two regions. It would be helpful if there could be a common complete application and not just a common form.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
Page 3 Guideline -Title -Introduction -Scope		Comment: (editorial) For clarity it may be better to include the broadened scope of a change to an existing designation in the title of the guideline and in the introduction section. Proposed change (if any): Title: "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, and on the change of an existing designation." Introduction: "Section H of this guideline also provides advice to sponsors wishing to change an existing designation of an orphan medicinal product." Scope: "This guideline also describes the information required by the EMEA to transfer the sponsorship of an orphan medicinal product designation, and to change an existing designation of an orphan medicinal product.".	
Page 5 Guideline Language		Comment: (editorial) It may be that an INN is not yet available at the time of the application for orphan designation, so some qualifying language could be added. Proposed change (if any): "-the name of the product (INN, if available, or common name)".	
Page 5 Guideline		Comment: (editorial) With regard to the sentence "The application should	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
Documentation to be supplied		contain about 30 pages", if it were intended to limit the size of the application it would be more appropriate to include a maximum number of pages. Also this sentence does not specify if the specified number of pages includes the application form, and/or any attachments and/or bibliographical references. Proposed change (if any): "The scientific part of the application should not exceed about 30 pages, excluding annexes/bibliography."	
Page 5 Guideline Information to be included in the application form (Annex)		Comment: (editorial) With regard to the sentence "An abbreviations list must be provided with each application." it is suggested to move this sentence to page 5 under "Information to be included in the scientific part of the application (Section A to E)", since this is not specific to the form, but rather to the application. Proposed change (if any): Move sentence to section "Information to be included in the scientific part of the application (Section A to E)".	
Page 5 Guideline 1. Name of the active substance		Comment: No additional text or change was included in this section. 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) would be helpful.	
Page 6 Guideline		Comment:	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
4. Sponsor /and contact person		(important) It is not understood what is meant practically by "Different applicants belonging to the same mother company or group of companies have to be taken as one entity." And to whom this is targeted (authorities or applicants). Should this be read in such a way that only one company belonging to a group of companies could apply for an orphan designation? Or should it be interpreted such that if an ODD is in the name of one applicant then the MAA can be in the name of another applicant as long as both ODD and MAA applicants belong to the same mother company or group of companies? Proposed change (if any):	
		Comment: (editorial) With regard to "The sponsor may be an individual or a company", this is redundant with the change to the previous paragraph. Proposed change (if any):	
Page 6 Guideline 5. Manufacturers		Comment: (important) The form is updated such that the name and address of the active substance manufacturer are no longer required. The guideline still indicates that manufacturers of both the active substance(s) and the medicinal product should be provided. Proposed change (if any): "The name(s) and address(es) of the manufacturer(s) and site(s) of manufacture of the ~~active substance(s) and of the~~	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
		medicinal product (if available) should be provided."	
Page 6 Guideline A. Description of the condition 2. Proposed therapeutic indication		Comment: (editorial) The title of this subsection has been changed from "orphan" to "therapeutic", while the text below the title details the "proposed orphan indication". This is confusing and it is suggested to revert the title back to "proposed orphan indication". Proposed change (if any): "2. Proposed orphan~~therapeutic~~ indication"	
		Comment: The text indicates that The sponsor should submit details of the proposed orphan indication … An ODD is requested and granted in an orphan condition. The indication is the claim at the time of MA application and is based on clinical results. This difference between condition and indication may cause confusion. Proposed change (if any):	
Page 7 Guideline A. Description of the condition 3. Medical Plausibility		Comment: The request to discuss the results of pre-clinical and preliminary clinical data could have the following implications: ☐ Timing of OD submission: This request could impact the timing of the submission of the OD application (delay it). Sponsors may have to wait with their OD application until they obtained sufficient data (pre-clinical and clinical) to support the use of the medicinal product in the intended orphan indication/ condition. Sponsors may lose the	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
		orphan incentives for early Protocol Assistance. · Bigger hurdle to obtain OD designation: OD designation is not granted anymore, based on a pure assumption. Data have to be provided to support the assumption that the product will work in the intended orphan indication/ condition. · Combined EU/US application: While COMP raises their requirements to obtain OD status with this revision, FDA still grants OD designations on pure assumptions. This makes a combined EU/US OD application redundant from the perspective of harmonization of timing of the OD applications, content of applications and maintenance of the EU/US OD designations.	
Page 7 Guideline A. Description of the condition 3. Medical Plausibility		Comment: (editorial) It is not clear what is meant with "as applied for in the specific condition". Was it intended to say "which are relevant to the proposed orphan indication"? Proposed change (if any): "It is important to include, as far as possible, a discussion of the results of pre-clinical studies with the specific product which are relevant to the proposed orphan indication,"	
		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. Therefore, to keep the possibility for sponsors to apply for an	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
		orphan designation at any stage of the development, it is proposed 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". It will allow 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.g. "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").	
		Comment: (important) A requirement was added that "All available studies should be submitted at the time of the application" and this could be interpreted to mean a requirement to submit all available study reports. While it may be important in the assessment to have a description of (the results of) all available studies, it will be burdensome and it will not provide added value to submit all study reports. This would also not be in line with what's indicated in section E, Description of the stage of development, i.e. that "The full study reports of non-clinical and clinical studies undertaken need not be provided unless requested." We propose to clarify this in the sentence as follows.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
		Proposed change (if any): "A summary of all available (non-)clinical study data should be included at the time of the application."	
Page 8 Guideline Special considerations		Compared to the previous version of the guideline, the case (c) was removed from the guideline: *"(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".* It is proposed that to consider keeping this specific case in the revised guideline as this special consideration seems to be relevant criteria for some specific orphan conditions.	
Page 9 Guideline B. Prevalence of the condition 1.2 Information from databases on rare diseases		Comment: (editorial) In this section an addition was made which is not clear: "and only case reports of the disease…". Was it meant to read: "and when only case reports of the disease are available…"? Proposed change (if any): "In the absence of epidemiological data or databases and when only case reports of the disease are available in the Union…"	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
Page 10 Guideline 2. Prevalence and incidence for the condition in the Union		A definition is provided for the prevalence in the first paragraph below section B. Additional clarity is sought by proposing to include a definition of incidence in this section.	
Page 12 Guideline D. Other methods for diagnosis, prevention or treatment of the condition 3. Justification of significant benefit		The implications of the request to provide a more detailed explanation of significant benefit over existing therapies; the justification on the potential increases in supply and availability; and critical review to justify significant benefit assumptions made at the time of OD application are seen as: • Bigger hurdle to obtain OD designation: Sponsor has to provide a detailed comparison with existing therapies at the time of the OD application, preferably with regard to clinically relevant benefits (no "soft" justification like "major contribution to patient care", but measurable benefits in clinical settings). E.g. Sponsor has to make detailed/ very concrete assumptions with regard to e.g. greater efficacy or improved PK behavior. · Higher risk to lose OD status at time of MAA: As the sponsor had to make more detailed/concrete assumptions on significant benefit at the time of the OD application, the risk to fail in clinical settings with regard to these	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
		assumptions is higher and therefore the risk to lose the OD designation at the time of MAA is higher, as well. · Potential delay of grant of MA: The critical review of the assumptions by COMP at the time of MAA may delay grant of MA. Comment: 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," It is suggested to add additional text to the end of the paragraph. Proposed change: "…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". "	
Page 12 Guideline D. Other methods for diagnosis, prevention or treatment of the condition 3. Justification of significant benefit		Comment: (important) With regard to "problems with a particular existing formulation", it is acknowledged that Commission Communication 2003/C 178/02 indicates that significant benefit may be based on "serious and documented difficulties with the formulation or route of administration of an authorised medicinal product". Further guidance would be useful as to when a difficulty is considered "serious". Also, it should be clarified if this relates specifically to 'similar active ingredients', or whether the scope is broader.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
		Proposed change (if any):	
Page 13 Guideline D. Other methods for diagnosis, prevention or treatment of the condition 3. Justification of significant benefit		Comment: (editorial) regarding the sentence "In all cases the COMP is required to assess whether or not these assumptions are plausible and are supported in the application by appropriate evidence.", considering that 'evidence' cannot in all cases be reasonably expected at an early stage of development, this term must be replaced by 'justification'. Proposed change (if any): "In all cases the COMP is required to assess whether or not these assumptions are plausible and are supported in the application by appropriate justification."	
		It is proposed to include 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". 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.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
		Indeed it would be useful as for the "*Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation*" document to also add a paragraph related to improvement of treatment compliance. 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.	
		Comment: (important) Section: "All designations based on the significant benefit criterion will be reviewed prior to the grant of a marketing authorization and after adoption of opinion by the CHMP. At the time the application for marketing authorisation is reviewed, sponsors of designated orphan medicinal products will be required to demonstrate significant benefit over currently authorised methods in order to maintain orphan status. At this stage, the COMP will require a higher level of data/evidence for the orphan status than at the time of designation to be maintained." The starting sentence implicates this only holds true for designations, which are based on 'significant benefit', which is not the case. This holds true to each and every orphan designation (e.g. to reconfirm eligibility based on prevalence,	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
		severity of the condition etc.). Proposed change (if any): "All orphan designations ~~based on the significant benefit criterion will be~~ are reviewed prior to the grant of a marketing authorization and after adoption of opinion by the CHMP at which time all accumulated evidence supporting the significant benefit criterion will be assessed. ~~At the time the application for marketing authorisation is reviewed,~~ Sponsors of designated orphan medicinal products will be required to demonstrate significant benefit over currently authorised methods in order to maintain orphan status. At this stage, the COMP will require a higher level of data/evidence for the orphan status to be maintained than at the time of designation ~~to be maintained~~."	
		Comment: (important) The sentence "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." was added but it is felt this extended detail offers for more questions and requires more guidance. Instead it may be better to emphasize to seek input from the EMA orphan office. Proposed change (if any):	
Guideline Page 13 Guideline		Comment: (editorial) Sentence: "The applicant should concisely describe	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
E. Description of the stage of development 1. Summary of the development of the product		the current development status of the orphan medicinal product within the Union, e.g. preliminary research, brief details of pharmaceutical development, tabular format of pre-clinical investigation, clinical investigation, final preparation of a marketing authorisation dossier, etc." Historically the term 'tabular format' refers to an extensive (up to 3-5 pages) tabular summary of each individual (non-clinical) study. Further clarification is requested if this is intended, or if an overview table of non-clinical studies is appropriate. Proposed change (if any):	
Page 14 Guideline G. Transfer of the Orphan designation to another sponsor and change in the name of the Sponsor and/or the address of the Sponsor 1. Transfer of the Orphan designation to another sponsor		Comment: (editorial) For consistency it would be good to include instructions around how to submit document electronically. Proposed change (if any): The sponsor should submit an application in electronic format to the EMA (orphandrugs@ema.europa.eu) accompanied by the following documentation:	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
Page 14 Guideline G. Transfer of the Orphan designation to another sponsor and change in the name of the Sponsor and/or the address of the Sponsor 1. Transfer of the Orphan designation to another sponsor		Comment: (important) By derogation to item 4, Sponsor/contact person on page 4, it must be clarified that if companies belong to the same mother company or group of companies and have to be taken as one entity, no prior transfer of orphan designation needs to take place if one company within that entity is the applicant of the MAA concerning an orphan designated product (MAH) for which another company within that entity is the sponsor of the orphan designation. A new sentence is to be added to clarify this. Proposed change (if any): "If companies belong to the same mother company or group of companies, these are taken as one entity. In this case, no prior transfer of orphan designation needs to take place if one company within that entity is the applicant of the MA concerning an orphan designated product (MAH) for which another company within that entity is the sponsor of the orphan designation."	
Page 15 Guideline H. Change of an existing designation.		The possibility to change an existing designation if additional scientific information becomes available and impacts the information included in the orphan designation is welcomed. However, it is proposed 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.)	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
Application Form		Comment: (editorial) As indicated for the Guideline, it may be better to include the broadened scope of a change to an existing designation in the title of the form. Proposed change (if any): See for "Guideline" above.	
Application Form		Comment: (editorial) Only the "Annex to Guideline on format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another (ENTR/6283/00)" was updated but not the "Common EMA/FDA form". For instance, the inclusion of a check box for "CHANGE OF AN EXISTING DESIGNATION" would have to be included in the FDA/EMA common form as well. Proposed change (if any):	
Application Form		Comment: (important) Additional questions and check boxes are included at the end of the form (section III-4, III-5, III-6 and III-7). It appears that the requested information is not essential for the (assessment of, and decision on, the) application for orphan medicinal product designation. Proposed change (if any): Removal of sections III-4, III-5, III-6 and III-7.	
Application Form Section III.7 Do		Comment: (important) See comments above; if left in, question III-7 is redundant for products that fall under the mandatory scope of	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome
you consider your product as an innovative medicinal product?		the Centralized Procedure, and this must be reflected in the question and the tick boxes. Proposed change (if any): III.7 Is your product covered under the mandatory scope of the centralized procedure or do you consider your product as an innovative medicinal product that will qualify for the centralized procedure? (please see definition on 'Guideline concerning the optional scope of the centralised procedure in accordance with Article 3(2)(b) of Regulation (EC) No 726/2004') * Mandatory scope * Therapeutic innovation * Scientific innovation * Technical innovation * No	

Please add more rows if needed.