

**EBE Comments on  
Revised Commission Guideline on  
“Format & Content of Applications for Designation as Orphan Medicinal Products & on the  
Transfer of Designations from one Sponsor to Another”**

The EBE members – many of which are researching and developing treatments for orphan conditions – would like to request that the European Commission take the following comments into consideration.

A general comment is that the present revision of the Guideline could be an opportunity to remedy some of the concerns about the current European orphan system. This would increase the numbers of orphan treatments being researched and increase the numbers of therapies available to patients suffering from rare diseases.

General suggestions in this regard are:

- The current prevalence calculation requirements create a potential obstacle to the development process, particularly for Small & Medium sized Enterprises (SMEs). The burden of proof of the rare prevalence is with the sponsor, therefore, methods of supporting this mechanism should be sought, e.g., the publication of lists of conditions which have already been deemed not to qualify according to the prevalence criteria or other such cooperative support.
- Translations are a large burden on SMEs – it was questioned what the value of developing a translation for the name of the rare indication in all (even small) European languages at this early stage would be.
- Bureaucratic requirements such as the need to provide 2 months’ notice should be reduced. Access to Protocol Assistance and fee-waiver procedures should be streamlined and available in a timely and straightforward manner.

### Specific Comments on the Guideline

Page 5 – “Information to be included in the remainder of the application”

The table of contents and check-list provided as part of the application form in the Annex can be used as a guide to complete the documentation submitted in an application for designation. In each section a **comprehensive** review of the relevant scientific literature should be included, supported and cross-referenced to published references. The following information should be provided:

Page 6 – Section A, Description of the Condition

1. Details of the Condition

Details of the condition that the medical product is intended to diagnose, prevent or treat should be provided. This information should provide a clear description of the disease or condition in question **based on published references. In certain conditions, literature-based description may not be possible, or may prove difficult. Description may be based on documentation from relevant experts.** Details of the causes and symptoms should be provided.

**Justification:** Self-explanatory.

### 3. Medical Plausibility

This section should be completed for all applications with details of the rationale for the use of the medicinal product in the proposed orphan indication. This should include a description of the medicinal product and *of the knowledge of* its mechanism of action *if possible*. It should be noted that to support the rationale for the development of the product in the proposed condition some preliminary preclinical or clinical data are generally required.

**Justification:** The mechanism of action of a medicinal product is not always known at the time of the application for designation.

#### General Comments:

- Based on the COMP's experience to date, it would also be helpful to have additional guidance on the types of preclinical or clinical data that could be considered as sufficient justification for the designation. When the medicinal product has not yet been administered in the clinical setting, the effects of the medicinal product in the preclinical models should be deemed acceptable.
- It would be very helpful if the Guidelines could give specific examples of diseases to better illustrate, and this would be particularly helpful in this section.

Page 7 – “General Requirements”

#### Sub-paragraph (c)

Different degrees of severity or stages of a disease would generally not be considered as distinct conditions *unless there is a rationale in a specific population, based on pathophysiological, histopathological or clinical specificities on the condition and on the mechanism of action of the product*.

**Justification:** The interpretation of this paragraph could be too restrictive; “generally” could be clarified by including this wording.

Page 8 – Section B, Prevalence of the Condition

#### Sub-Paragraph 1.1

The documentation should include a *comprehensive* review of authoritative references which demonstrate that the disease or condition for which the medicinal product would be administered, affects not more than five in 10,000 persons in the Community.

**General Comment:** What will the impact of the enlarged Community be on the calculation / extrapolation of the prevalence, for the already-designated medicinal products when the re-evaluation of the designation takes place?

Page 9 – Section C, Potential for Return on Investment

General Comment: What are the consequences if a sponsor fulfilled all the requirements for a successful application, but later in the course of this procedure, either:

- a) The COMP does not consider the drug “approvable” for orphan drug designation; or
- b) The sponsor might have to withdraw its application for one reason or another.

**General Comment:** Will these pre-investments also be considered in the light of “potential for return on investment” for subsequent applications irrespective of the earlier application, even for the same orphan disease?