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Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation

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Introduction

According to the European Parliament and Council Regulation (EC) 141/2000 (Art 5) and the Commission Regulation (EC) 847/2000 "a sponsor applying for designation of a medicinal product shall apply for designation at any stage of the development of the medicinal product before the application for marketing authorization is made". Furthermore, in the criteria for designation (Article 3 of Regulation (EC) 141/2000) it is stated that a medicinal product shall be designated as an orphan medicinal product if its sponsor can establish that "there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the European Union or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition".

This Discussion Paper has two aims. Firstly, to outline the level of evidence normally required to support the medical plausibility of using the product in the applied condition, and secondly, the level of evidence required to support the assumption of significant benefit. The paper is based on the experience accumulated over recent years with several hundred orphan drug designation applications, approximately 70% of which included a discussion on significant benefit since satisfactory methods for diagnosis, prevention or treatment existed in the European Union at the time of the submission of the application.

General guidance is already available on what is considered necessary to support 'medical plausibility' at the time of the submission of an orphan designation application and on what is necessary for the justification of the assumption of 'significant benefit' if this criterion applies. This is included in the "Commission 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" (ENTR/6283/00) and in the "Communication from the Commission on Regulation (EC) 141/2000 of the European parliament and of the Council on orphan medicinal products" (Commission Communication 2003/C 178/02 of 29 July 2003). This discussion paper should be read in conjunction with these documents.

According to the Commission Guideline (ENTR/6283/00), the medical plausibility section should be completed for all applications. There are two aspects to "Medical Plausibility":

- (1) the rationale for use of the medicinal product in the proposed orphan indication; and
- (2) where the orphan indication refers to a subset of a particular condition, a justification of the medical plausibility for restricting the medicinal product in the sub-set.

The 'rationale for development' is closely and necessarily linked with both the nature of an orphan drug as a 'medicinal product' and with the designation criterion set out in Article 3.1(a) of Regulation (EC) No 141/2000.

A product which is the subject of such application must be a medicinal product as defined in Article 1, Directive 2001/83/EC and consideration of the 'medical plausibility' at an early stage of product development provides a means of verifying this. Article 3.1 which lays down the criteria for designation states that "*a medicinal product shall be designated as an orphan medicinal product if its sponsor can establish: that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition....*". Based on this wording, the Committee for Orphan Medicinal Products (COMP) will consider the notion of 'medical plausibility' when assessing an application for designation.

The Commission Communication (2003/C 178/02) section B.1, furthermore, recognises that the COMP may take into account available data to modify the condition under application (for example, because the Committee considers that the designatable condition is broader than the one under application). To define a suitable condition for designation, the COMP must look at the rationale for development of the medicinal product in the proposed orphan indication. This is imperative to prevent the slicing of common conditions into invalid sub-sets (e.g. different stages of a condition such as “metastatic cancer”; subgroups of frequent diseases where the product would have interest in the rest of the disease; conditions defined based on the therapeutic use of the product such as “treatment in patients not responding to X”). It is important that sponsors, when preparing designation applications, are aware that this is an important issue that will be reviewed by the Committee.

It should be noted that for the purpose of designation and to support the rationale for the development of the product in the proposed condition some preliminary preclinical or clinical data are generally required. A pharmacological concept, not supported by any form of evidence, would generally not be considered by the COMP as sufficient justification for the designation of the medicinal product in the proposed condition.

Article 3(1)b of Regulation EC 141/2000 states that in the case where a satisfactory method of diagnosis, prevention or treatment of the condition exists, the sponsor has to establish ‘that the medicinal product will be of significant benefit to those affected by that condition’. In the Commission Communication it is stated, “a treatment for a particular disease or condition may be associated with certain risks. These risks are balanced against the expected benefits when considering whether to grant or refuse a marketing authorisation in accordance with the criteria of safety, quality and efficacy as laid down in Directive 2001/83/EC. A marketing authorisation is granted if the benefit risk assessment is positive”. As mentioned in the Commission Regulation (EC) 847/2000, authorised medicinal products are therefore considered satisfactory methods of diagnosis, prevention or treatment. Commonly used methods of diagnosis, prevention or treatment that are not subject to marketing authorization (e.g. surgery, medical devices) may be also considered satisfactory methods, if there is scientific evidence as to the value of those methods.

Significant benefit is defined in Commission Regulation (EC) 847/2000 as ‘a clinically relevant advantage or a major contribution to patient care.’ The applicant is required to justify the assumption that the medicinal product will be of significant benefit compared to the existing authorized medicinal products or methods at the time of designation.

As there may be little or no 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. As stated in the Guideline (ENTR/6283/00), at the time of designation “significant benefit should be based on well justified assumptions. Assumptions of potential benefit(s) should be plausible and where possible based on sound pharmacological principles.” In the same Guideline it is also stated that “In general a demonstration of potentially greater efficacy, an improved safety profile, and/or more favourable pharmacokinetic properties than existing methods may be considered to support the notion of significant benefit.”

In addition, the Commission Communication on Regulation (EC) No 141/2000 gives some clarification on the possibility to base the significant benefit on the availability of the medicinal product (e.g. European Union availability versus availability in one Member State; supply insufficient to meet patients’ needs with the exclusion of either transient or artificial problems in supply), documented safety problems in relation to the origin of the medicinal product; serious and documented difficulties with the formulation or route of administration; long term interruption in supply of an authorized product; favorable and clinically relevant pharmacokinetic properties. 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.

Supporting data and references

Generally for the justification of the medical plausibility and the assumption of significant benefit it is a requirement that the sponsor's argument should be substantiated by appropriate scientific documentation. When possible, cross-references to the literature, preferably peer-reviewed, should be added and listed separately. Other forms of literature references or unpublished reports and expert statements may also be used.

Medical Plausibility

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. As a general rule at least relevant *in vitro* and *in vivo* data in appropriate preclinical models should be submitted. If available, established *in vivo* models for the global condition should preferably be used. If *in vitro* evidence only is available at the time of the application, the relevance of the findings should be discussed in the context of the proposed condition. When available, comparative data or a discussion comparing the results obtained with the product to those obtained with comparators should be provided. The preclinical data should be discussed in full even if preliminary results from first administration to humans are available. Furthermore, the application should contain a brief outline on the future plans regarding the preclinical development; future studies should be easily distinguishable from studies already performed or ongoing.

If the product is developed for additional conditions other than the orphan indication applied for, a very brief description of the *in vitro* and *in vivo* preclinical data should be included but should be clearly separated from the preclinical data which are relevant for the proposed orphan condition.

Clinical data from studies in the proposed condition, if available, should be presented separately from clinical data in other conditions in order to clearly differentiate them from studies in other conditions. Only data applicable to the proposed orphan indication should be presented in detail.

In addition to the efficacy data, a summary of any available important safety data obtained in the preclinical and clinical setting (both in the orphan condition and in other conditions) should be included in the application.

Justification of the assumption of significant benefit

When the application is based on an assumption of significant benefit, a comparison with authorized treatments or otherwise established methods is required for designation, as opposed to applications for conditions where there are no available means of diagnosis, prevention, or treatment or for a condition for which the available methods are not considered satisfactory.

To follow the spirit of the Orphan legislation, which makes it clear that an orphan application may be made at any stage of the development, 'significant benefit' will be based on the available evidence at the stage of designation. Acknowledging the fact that many sponsors will apply for orphan designation at an early stage in development, when comparative data are often not available, a critical review comparing authorised treatments and the proposed Orphan Medicinal Product and justifying the

assumption of significant benefit should be provided. This review should be based not only on the limitations and risks of the authorised products but also on the benefit expected with the proposed product.

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. The assessment of significant benefit before marketing authorization is made exclusively by the COMP and the procedure runs without interferences with the marketing authorization application assessment. At this stage, the COMP will require a higher level of evidence than at the time of designation for the orphan status to be maintained.

For a claim of 'significant benefit', i.e. a clinically relevant advantage or major contribution to patient care to be sustained, the COMP will evaluate whether there is a high probability for the patients to experience a clinically relevant benefit. Thus, it has to be concrete and based on the data contained in the application for marketing authorisation and the arguments presented by the sponsor. After adoption of the opinion from the CHMP collaboration between the committees could be sought if necessary in order to assure consistency and collaboration between scientific committees at the European Medicines Agency as stated in the pharmaceutical regulation (articles 56(1) and 64(2) of Regulation (EC) No 726/2004).

Significant benefit based on an assumption of improved efficacy

If the proposed product has not yet been administered in the clinical setting, the effects of the product in the preclinical models should be discussed in comparison with the effects of authorized treatments or established methods in the same models. In the absence of any data in the proposed condition, the fact that the proposed product may have a different mechanism of action is not considered sufficient by itself to justify the assumption of significant benefit. Based on the evidence available, the sponsor should justify that the mechanism of action may translate into an improved efficacy in order to support the assumption of significant benefit (e.g. targeting two receptors instead of one for the treatment of the same condition would not be seen as significant benefit per se if the additional pharmacological target does not result in improved efficacy or safety). If nonclinical models are used, it is preferable that the comparison is derived from direct comparative experiments rather than from results published in the literature.

If clinical data exist, it is acknowledged that results from comparative clinical trials may not be available at the time of submission of the orphan designation application. Therefore presentation of the effects observed in exploratory studies and comparison with the data available in the literature may be appropriate to justify the assumption of significant benefit. In some situations quantitative methods for indirect comparison may be used.

Very preliminary clinical results in a small number of patients will be taken into consideration with caution by the COMP as important limitations apply to the interpretation of such initial results. When positive preclinical data are not consistent with preliminary clinical results, particular attention will be drawn to the predictive value of the preclinical models, and the number of species and models tested compared to the extent and predictive value of the preliminary clinical results. If, after considering these and other potentially important aspects of the experience accumulated at the time of designation, there is a situation in which the pharmacological concept is sound and the evidence in relevant preclinical models is compelling, the designation could be granted on the basis of an assumption of significant benefit even if the preliminary clinical results are not convincing. The significant benefit will be reassessed by the COMP before the granting of the Marketing Authorization, when complete clinical data are submitted.

Significant benefit based on an assumption of improved safety

The safety profile of a medicinal product is usually fully characterized after a medicinal product is placed on the market, since rare adverse events can only be observed after administration of the product to many patients under normal conditions of use. Therefore, if significant benefit is based on expectations of a clinically relevant improved safety profile, the reasons for these expectations must be clearly justified, either by clinical experience or exceptionally by reference to the pharmacological properties of the medicinal product.

One example where safety may be argued to justify an assumption of significant benefit would be where a medicinal product which is already authorised for another indication is then developed for a new orphan indication. In such a case if the current methods for the proposed orphan indication have significant safety problems, which are documented, the sponsor of the proposed medicinal product may argue significant benefit based on the knowledge of the safety profile of the product in the authorised indications. The possibility of extrapolating the safety data obtained from the authorized indication to the proposed orphan population should be fully discussed in the application.

Where safety is argued to justify significant benefit, it is important that safety issues with current methods are documented and not just theoretical. For example, on several occasions attempts to justify the assumption of significant benefit of recombinant or transgenic products have been based on the risk of viral transmission with plasma-derived products. According to the Commission Communication, generally if the risk is theoretical and there are no observed and documented cases of viral transmission with the authorised and used plasma derived products, it is not possible to base the assumption of significant benefit on an assumption of expected improved safety, since as mentioned above the safety profile is only established relatively late in the development when broad human exposure has taken place. A theoretical risk with an authorised product cannot be compared with a theoretical lack of risk with the product under development. The potential for antigenicity associated with a new transgenic product may, for example, pose a greater risk than the potential for viral transmission associated with a blood derived product which has been safely on the market for two or three decades. As mentioned in the Commission Communication, enhancement of the pharmaceutical quality of a product in compliance with the relevant guidelines does not constitute a basis for the assumption of significant benefit (e.g. implementing a new purification step or an additional step in the production to avoid viral transmission).

In some cases the authorised treatments are associated with certain adverse events linked to the route of administration. In such cases the assumption of significant benefit for a different product may be based on another route of administration generally associated with less risk.

Significant benefit based on an assumption of a major contribution to patient care

Significant benefit based on an assumption of a major contribution to patient care has also been used for orphan designation. Based on the experience accumulated over recent years, assumptions have mainly been based on more convenient modes of administration improving patient compliance or on improved availability of the product for the patient population. Other arguments that may improve the quality of life of the patients may also be considered for this purpose.

In the former case the discussion on the route of administration should focus on the condition and the current treatment modalities, i.e. ease of self-administration may be important in ambulant patients but less so in patients likely to be hospitalized during treatment. In some cases a new route of administration may also be viewed as an improvement in safety. For example, if current treatments

have to be administered via a central intravenous catheter and the proposed treatment is for pulmonary or oral administration. However, clinical data should generally be available to support such argumentation, because a theoretical advantage e.g. of administration by inhalation may be counterbalanced by the induction of severe bronchoconstriction or, conversely, a product administered orally may have severe gastrointestinal toxicity.

With regard to availability as an argument to support a major contribution to patient care, the Commission Communication clarifies the possibility of basing the significant benefit on the improved supply/availability of the medicinal product. In the evaluation of the issue of the availability the COMP will discuss and conclude as to whether justifications provided by the sponsor on the potential increase in supply/availability could be translated into a clinically relevant potential significant benefit for the patient population in all Member States.

Significant benefit prior to the grant of the marketing authorization

Demonstration of significant benefit at the time of marketing authorisation will need to be supported by data and a critical review of the clinically relevant advantage or major contribution to patient care that the product may offer in the context of the methods authorized for the proposed orphan indication. It is expected that most of the data to demonstrate significant benefit will be generated during the clinical development of the product. The sponsor is expected to comply with established guidelines on development of products in 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 authorized products in the orphan condition even if comparative clinical studies are not always required or possible.

In this respect, sponsors are strongly advised to seek protocol assistance to discuss how to generate the necessary data.

If the protocol assistance with regards to the significant benefit justification is not followed the sponsor will be asked to justify the deviation from the advice given.