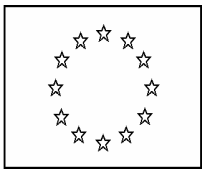

EUROPEAN COMMISSION

ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Brussels, November 2007

GUIDANCE ON ELEMENTS REQUIRED TO SUPPORT THE SIGNIFICANT CLINICAL BENEFIT IN COMPARISON WITH EXISTING THERAPIES OF A NEW THERAPEUTIC INDICATION IN ORDER TO BENEFIT FROM AN EXTENDED (11-YEAR) MARKETING PROTECTION PERIOD

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1. Introduction

Article 14(11) of Regulation (EC) No 726/2004 states: "Without prejudice to the law on the protection of industrial and commercial property, medicinal products for human use which have been authorised in accordance with the provisions of this Regulation shall benefit from an eight-year period of data protection and a ten-year period of marketing protection, in which connection the latter period shall be extended to a maximum of 11 years[1] if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies". The new periods of protection only apply to reference medicinal products for which an application for authorisation has been submitted after 20 November 2005 (Article 89 of Regulation (EC) No 726/2004).

Article 10(1) fourth subparagraph of Directive 2001/83/EC as amended by Directive 2004/27/EC states: "The ten-year period referred to in the second subparagraph shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies".[2]

[1] Note: Generic medicinal products may still be submitted after 8 years have elapsed from the initial authorisation of the original product.

[2] It should also be noted that Article 36(5) of Regulation EC (No) 1901 (the paediatric regulation) states: "In the case of an application under Article 8 which leads to the authorisation of a new paediatric indication, paragraphs 1, 2 and 3 shall not apply if the applicant applies for, and obtains, a one-year extension of the period of marketing protection for the medicinal product concerned, on the grounds that this new paediatric indication brings a significant clinical benefit in comparison with existing therapies, in accordance with Article 14(11) of Regulation (EC) No 726/2004 or the fourth subparagraph of Article 10(1) of Directive 2001/83/EC".

The aim of this guidance is to outline the level of evidence required to support extended marketing protection period based on a new therapeutic indication held to bring a significant clinical benefit in comparison with existing therapies as referred to in Article 14(11) of Regulation (EC) No 726/2004 or Article 10(1) fourth subparagraph of Directive 2001/83/EC.

2. Principles and procedure

In order to benefit from the extended period of marketing protection, the authorisation of the new indication should take place within eight years from the date of the first authorisation.

MAHs are encouraged to contact the EMEA or national competent authority in advance of the submission if clarification on the timetable for the procedure is needed.

The MAH should provide the authority assessing the application with any relevant information for the assessment of the significant clinical benefit of a new indication, in accordance with Article 14(11) of Regulation (EC) No 726/2004 or Article 10(1) fourth subparagraph of Directive 2001/83/EC. Such documentation should be submitted in Module 1 *(See Notice to Applicants)* of the application for marketing authorisation; related study reports and literature references should be placed in relevant Modules of the dossier and cross-referred to, accordingly.

The CHMP or National Competent Authority will assess the significant clinical benefit in comparison with existing therapies in parallel to the evaluation of the quality, safety and efficacy of the medicinal product in the new indication. Such assessment will be performed within the normal marketing authorisation assessment timelines. Where necessary, questions on the significant clinical benefit in comparison with existing therapies will be part of the list of questions/request for supplementary information to be addressed by the MAH.

For products submitted for a centralised marketing authorisation, the CHMP will adopt a single opinion, which will cover both the significant clinical benefit in comparison with existing therapies, and the scientific assessment of the new indication for the purpose of authorisation. The MAH may ask for re-examination of the CHMP opinion following the usual conditions for re-examination after an opinion (Article 9(2) of Regulation (EC) No 726/2004). The findings of significant clinical benefit in comparison with existing therapies will be described in the European Public Assessment Report.

3. General guidance on the preparation of the report justifying that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies

The MAH should provide, in the form of a report, the information referred to above, allowing to establish whether the medicinal product will be of significant clinical benefit in comparison with existing therapies in the new therapeutic indication. In the case of new indications for which there are no existing therapies relating to the proposed new therapeutic indication in the Community the MAH should submit information to establish this.

The report should include:

- Justification of the proposed new indication compared to the therapeutic indication(s) already authorised.

- Details of existing therapies relating to the proposed new indication

- Justification as to why the medicinal product, for which extended marketing protection period is sought, is of significant clinical benefit in comparison to existing therapies in the new therapeutic indication.

3.1 New indication

For the purpose of this guideline, a “new therapeutic indication” may refer to either diagnosis, prevention or treatment of a disease. The MAH should provide a justification for the proposed new indication, supported by appropriate scientific information.

No definition of new indication exists in Community legislation, however, Notice to Applicants "A Guideline on Summary of Product Characteristics" states in its section 4.1 "The indication(s) should be stated clearly and concisely and should define the target disease or condition distinguishing between treatment (symptomatic, curative or modifying the evolution or progression of the disease), prevention (primary or secondary) and diagnostic indication. When appropriate it should define the target population especially when restrictions to the patient populations apply".

In this context a new indication would normally include the following:

- a new target disease,
- different stages or severity of a disease
- an extended target population for the same disease, e.g. based on a different age range or other intrinsic (e.g. renal impairment) or extrinsic (e.g. concomitant product) factors
- change from the first line treatment to second line treatment (or second line to first line treatment), or from combination therapy to monotherapy, or from one combination therapy (e.g. in the area of cancer) to another combination,
- change from treatment to prevention or diagnosis of a disease.
- change from treatment to prevention of progression of a disease or to prevention of relapses of a disease.
- change from short-term treatment to long-term maintenance therapy in chronic disease.

3.2 Details of existing therapies

Existing therapies means satisfactory methods of diagnosis, prevention or treatment of the disease in question. These may include authorised medicinal products, as well as other established methods.

The MAH should review and detail the characteristics of existing therapies (available diagnosis, prevention or treatment methods) in the Community, making reference to marketing authorisations, scientific and medical literature or other relevant information. If no other methods currently exist, this should be stated.

It should be noted that the claim of significant clinical benefit in comparison to existing therapies will have to take into account all existing products at the time of the relevant application.

The review should include medicinal products authorised in at least one Member State (national or mutual recognition procedures) or by the Community (centralised procedure). Authorised medicinal products will generally be considered satisfactory existing therapies.

The MAH should also consider non-pharmacological approaches to the diagnosis, prevention or treatment of the disease in question, as appropriate, such as surgical interventions, radiological techniques, diet, psychotherapy, physical means, and other specific and non-specific therapeutic methods which are considered 'state-of-the art' treatment for the indication in question in the Community. The review should make reference to the scientific and medical literature or any other relevant information to describe the value of such methods. If the MAH considers that the currently available methods of diagnosis, prevention or treatment cannot be considered as satisfactory existing therapies, it should justify why the methods are considered unsatisfactory. This may be based on clinical information, on scientific literature, or lack of availability of such methods.

The MAH should provide background information on medicinal products that are not authorised in the Community if they are widely recognised and used by the medical community.

3.3. Justification of significant clinical benefit

The MAH should provide scientific data and documentation establishing that the medicinal product for which the extended marketing protection period is sought is of significant clinical benefit in comparison with existing therapies. The justification should generally be supported by results of comparative clinical studies. The choice of the comparator (existing therapy) in clinical trial(s) should be justified by relevant scientific literature, CHMP guidelines, or scientific advice from competent authorities. Placebo controlled studies or even uncontrolled studies may be sufficient to justify significant clinical benefit only in the unusual event of exceptional benefit which could not be due to chance or a confounding factor. Other scientific literature, unpublished reports and expert statements would normally only be considered as supportive evidence.

A new treatment could generally be of significant clinical benefit if it provides a clinically relevant advantage or major contribution to patient care. In general, demonstration of greater efficacy, improved safety profile, and/or more favorable pharmacokinetic properties resulting in demonstrable clinical advantages compared to existing methods may support the notion of significant clinical benefit. It is noteworthy that the CHMP or National Competent Authority will evaluate the claims for significant clinical benefit in comparison to existing therapies on a case-by-case basis.

<u>3.3.1 Significant clinical benefit based on improved efficacy</u>

Efficacy greater than that of an authorised medicinal product should be assessed using clinically meaningful endpoint(s) in adequate and well-controlled clinical trials. Generally, this would represent the same level of evidence needed to support a comparative efficacy claim for two different medicinal products. Direct comparative clinical trials are normally preferred.

3.3.2. Significant clinical benefit based on improved safety

Significant clinical benefit based on improved safety should be clearly justified and would normally require to be substantiated by large and robust data. This is because the safety profile of a medicinal product is usually fully characterised only after a medicinal product is placed on the market (rare – but possibly serious - adverse reactions can be observed only after administration of the product to many patients under normal conditions of use). Thus, the relative safety profile will have to be globally assessed compared to existing therapy(ies), preferably through comparative trial(s). In addition, if a particular safety benefit was to be expected, this should normally be shown in a specific, prospective study quantifying the risk for each therapy.

Where significant clinical benefit is based on improved safety, no important reduction in benefit should be seen thereby making less favourable the overall benefit risk balance.

The relevance of extrapolating safety data obtained from the authorised therapeutic indication to the proposed new indication to support a safety benefit should be justified in the application.

3.3.3. Significant clinical benefit based on major contribution to patient care

A new mode of administration (in the new indication) could be considered a clinical benefit. In this case the MAH's justification should focus on the disease and current treatment modalities, e.g. ease of self-administration may be important in ambulant patients, but less so in patients likely to be hospitalised during treatment. In some cases, a new route of administration may also be viewed as improvement in safety (e.g. current treatments have to be administered via a central intravenous catheter and the proposed treatment is for topical or oral administration). However, clinical data would normally need to be available to support such arguments.

Even without showing greater efficacy or greater safety, a medicinal product having shown a benefit risk balance at least similar to existing therapies could be considered of significant clinical benefit if it acts through a different principal mechanism of action and thus provides a treatment alternative, or it produces a response different from other treatments in a substantial part of the targeted population.

4. Scientific advice from competent authorities on the development of a product in a new indication expected to bring significant clinical benefit compared to existing therapies.

It is recommended that, in cases of doubt, the MAH request scientific advice from EMEA or National competent authorities, at an appropriate time, when designing trials to assess safety and efficacy in a new indication expected to bring significant clinical benefit compared to existing therapies.