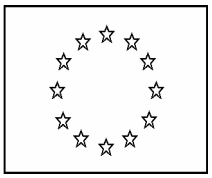

EUROPEAN COMMISSION

ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

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GUIDANCE ON A NEW THERAPEUTIC INDICATION FOR A WELL-ESTABLISHED SUBSTANCE

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Table of contents

1. Introduction

Paragraph 5 of Article 10 of Directive 2001/83/EC, as amended by Directive 2004/27/EC, states that where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication.

The aim of this guidance is to describe "significant preclinical or clinical studies" and to outline the principles and procedure for the assessment.

2. Principles and procedure

Applicants for a new therapeutic indication should provide the authority assessing the application with any relevant information for the assessment of whether the application concerns "a new therapeutic indication" and whether "significant preclinical or clinical studies" have been carried out in relation to this new indication.

This information should be presented in the form of a report and this should be included in Module 1 of the application for marketing authorisation; related study reports and supporting literature references should be placed in relevant modules of the dossier and cross-referred to accordingly. If the product has been granted access to the Centralised Procedure, the EMEA scientific committees will assess whether significant preclinical or clinical studies have been carried out in relation to this new indication. Likewise the reference member state will make this assessment for applications to the mutual recognition and decentralised systems and the relevant national competent authority will conduct the assessment for purely national applications. This assessment will be performed as part of the procedure within the normal timelines laid down in legislation. Where necessary, questions on the significance of studies may be part of the request for supplementary information to be addressed by the applicant.

For applications for centralised marketing authorisations the Committee on Human Medicinal Products shall adopt a single opinion, which will cover whether significant preclinical or clinical studies have been carried out in relation to the new indication, with the opinion on the scientific assessment of the new indication for the purpose of authorisation. The applicant may ask for re-examination of the opinion following the usual conditions and procedures for re-examination of an opinion (Article 9(2) of Regulation (EC) No 726/2004).

The findings of "significant pre-clinical or clinical studies" will be described in the European Public Assessment Report.

3. General guidance on the preparation of the report justifying that significant preclinical or clinical studies have been carried out in relation to the new indication

The justification that significant preclinical or clinical studies have been carried out in relation to the new indication should be in the form of a short report (in general not more than 5-10 pages), which should include:

- Introduction

- Justification of the new indication compared to the existing therapeutic indication(s):

For the purpose of the implementation of Article 10(5), 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.

- Justification that significant preclinical or clinical studies have been carried out in relation to the new indication:

The significance of the preclinical or clinical studies will be evaluated by the EMEA scientific committees or National Competent Authority on a case-by-case basis, however, guiding principles are:

- The applicant should summarize in this report the new preclinical and/or clinical studies carried out in relation to the new indication, and why these should be viewed as significant preclinical or clinical studies.

- The applicant should include his own preclinical and/or clinical studies into the dossier. “Own” means that such investigations have been conducted or sponsored by the applicant.

- In principle, when applying for marketing authorisation for a new indication, it is expected that the applicant has carried out at least one confirmatory clinical trial versus a suitable comparator in the new indication. This trial would be considered as a significant clinical study.

- However, as standard requirements for granting a marketing authorisation for a new indication are applicable, further data including preclinical or clinical pharmacological and further confirmatory clinical trial(s) may also be required for granting a marketing authorisation.

- Exceptionally, other preclinical or clinical studies performed by the applicant could be considered significant if they allowed the use of existing or published data (e.g. clinical trials) to support the marketing authorisation application in the new indication. Significance of these preclinical or clinical studies will be evaluated by the EMEA scientific committees or National Competent Authority on a case-by-case basis. To be considered significant in this situation, preclinical or clinical studies should have been relevant and necessary to the approval of the marketing authorisation application in the sought indication; it is the quality (importance of the data in relation to granting of a marketing authorisation in the new indication), rather than the quantity of the data, which will normally determine the significance of these preclinical or clinical studies.

4. Scientific advice from competent authorities

It is recommended that, in cases of doubt, to request scientific advice from EMEA or National Competent Authorities when designing trials to assess safety and efficacy in a new indication expected to benefit from one-year data exclusivity in accordance with Article 10(5).