

[^{F1}ANNEX I

ANALYTICAL, PHARMACOTOXICOLOGICAL AND CLINICAL STANDARDS AND PROTOCOLS IN RESPECT OF THE TESTING OF MEDICINAL PRODUCTS

Textual Amendments

- F1** Substituted by [Commission directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use \(Text with EEA relevance\)](#).

PART II

SPECIFIC MARKETING AUTHORISATION DOSSIERS AND REQUIREMENTS

Some medicinal products present specific features which are such that all the requirements of the marketing authorisation application dossier as laid down in Part I of this Annex need to be adapted. To take account of these particular situations, an appropriate and adapted presentation of the dossier shall be followed by applicants.

1. WELL-ESTABLISHED MEDICINAL USE

For medicinal products the active substance(s) of which has/have a ‘well-established medicinal use’ as referred to Article 10(1)(a)(ii), with recognised efficacy and an acceptable level of safety, the following specific rules shall apply.

The applicant shall submit Modules 1, 2 and 3 as described in part I of this Annex.

For Modules 4 and 5, a detailed scientific bibliography shall address non-clinical and clinical characteristics.

The following specific rules shall apply in order to demonstrate the well-established medicinal use:

- a) Factors which have to be taken into account in order to establish a well-established medicinal use of constituents of medicinal products are:
- the time over which a substance has been used,
 - quantitative aspects of the use of the substance,
 - the degree of scientific interest in the use of the substance (reflected in the published scientific literature) and
 - the coherence of scientific assessments.

Therefore different periods of time may be necessary for establishing well-established use of different substances. In any case, however, the period of time required for establishing a well established medicinal use of a constituent of a medicinal product must not be less than one decade from the first systematic and documented use of that substance as a medicinal product in the Community.

- b) The documentation submitted by the applicant should cover all aspects of the safety and/or efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favourable

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and unfavourable, must be communicated. With respect to the provisions on ‘well-established medicinal use’ it is in particular necessary to clarify that ‘bibliographic reference’ to other sources of evidence (post marketing studies, epidemiological studies, etc.) and not just data related to tests and trials may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.

- c) Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking.
- d) The non-clinical and/or clinical overviews must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorisation has been made in spite of the existing differences.
- e) Post-marketing experience with other products containing the same constituents is of particular importance and applicants should put a special emphasis on this issue.

2. ESSENTIALLY SIMILAR MEDICINAL PRODUCTS

- a) Applications based upon Article 10(1) (a) (i) (essentially similar products) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex provided the applicant has been granted the consent of the holder of the original marketing authorisation to cross refer to the content of his Modules 4 and 5.
- b) Applications based upon Article 10(1) (a) (iii) (essentially similar products i.e. generics) shall contain the data described in Modules 1, 2 and 3 of Part I of this Annex together with data showing bio-availability and bio-equivalence with the original medicinal product provided the latter is not a biological medicinal product (see Part II, 4 Similar biological medicinal products).

For these products the non-clinical/clinical overviews/summaries shall particularly focus on the following elements:

- the grounds for claiming essential similarity;
- a summary of impurities present in batches of the active substance(s) as well as those of the finished medicinal product (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed together with an evaluation of these impurities;
- an evaluation of the bio-equivalence studies or a justification why studies were not performed with respect to the guideline on ‘Investigation of Bio-availability and Bio-equivalence’;
- an update of published literature relevant to the substance and the present application. It may be acceptable for articles in ‘peer review’ journals to be annotated for this purpose;
- every claim in the summary of product characteristics not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies.
- if applicable, additional data in order to demonstrate evidence on the equivalence of safety and efficacy properties of different salts, esters or derivatives of an authorised active substance should be provided by the applicant when he claims essential similarity.

3. ADDITIONAL DATA REQUIRED IN SPECIFIC SITUATIONS

Where the active substance of an essentially similar medicinal product contains the same therapeutic moiety as the original authorised product associated with a different salt/ester complex/derivative evidence that there is no change in the pharmaco-kinetics of the moiety, pharmaco-dynamics and/or in toxicity which could change the safety/efficacy profile shall be demonstrated. Should this not be the case, this association shall be considered as a new active substance.

Where a medicinal product is intended for a different therapeutic use or presented in a different pharmaceutical form or to be administered by different routes or in different doses or with a different posology, the results of appropriate toxicological and pharmacological tests and/or of clinical trials shall be provided.

4. SIMILAR BIOLOGICAL MEDICINAL PRODUCTS

The provisions of Article 10(1)(a) (iii) may not be sufficient in the case of biological medicinal products. If the information required in the case of essentially similar products (generics) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided.

When a biological medicinal product as defined in Part I, paragraph 3.2 of this Annex, which refers to an original medicinal product having been granted a marketing authorisation in the Community, is submitted for a marketing authorisation by an independent applicant after the expiry of data protection period, the following approach shall be applied.

- Information to be supplied shall not be limited to Modules 1, 2 and 3 (pharmaceutical, chemical and biological data), supplemented with bio-equivalence and bio-availability data. The type and amount of additional data (i.e. toxicological and other non-clinical and appropriate clinical data) shall be determined on a case by case basis in accordance with relevant scientific guidelines.
- Due to the diversity of biological medicinal products, the need for identified studies foreseen in Modules 4 and 5, shall be required by the competent authority, taking into account the specific characteristic of each individual medicinal product.

The general principles to be applied are addressed in a guideline taking into account the characteristics of the concerned biological medicinal product published by the Agency. In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.

5. FIXED COMBINATION MEDICINAL PRODUCTS

Applications based upon Article 10 (1) (b) shall relate to new medicinal products made of at least two active substances not previously authorised as a fixed combination medicinal product.

For those applications a full dossier (Modules 1 to 5) shall be provided for the fixed combination medicinal product. Where applicable, information regarding the manufacturing sites and the adventitious agents, safety evaluation shall be provided.

6. DOCUMENTATION FOR APPLICATIONS IN EXCEPTIONAL CIRCUMSTANCES

When, as provided for in Article 22, the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

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- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- in the present state of scientific knowledge, comprehensive information cannot be provided, or
- it would be contrary to generally accepted principles of medical ethics to collect such information,

marketing authorisation may be granted subject to certain specific obligations.

These obligations may include the following:

- the applicant shall complete an identified programme of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit/risk profile,
- the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radio-pharmaceutical, by an authorised person,
- the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

7. MIXED MARKETING AUTHORISATION APPLICATIONS

Mixed marketing-authorisation applications shall mean marketing-authorisation application dossiers where Module 4 and/or 5 consists of a combination of reports of limited non-clinical and/or clinical studies carried out by the applicant and of bibliographical references. All other Module(s) are in accordance with the structure described in Part I of this Annex. The competent authority shall accept the proposed format presented by the applicant on a case by case basis.]