

## [<sup>F1</sup>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

#### 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 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

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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.]