The rules governing medicinal products
in the European Union

Volume 2B

Notice to Applicants

Medicinal products for human use

Presentation and content of the dossier

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Pharmaceuticals and cosmetics

THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN UNION

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FOREWORD

This Notice to Applicants (NTA) has been prepared by the European Commission, in consultation with the competent authorities of the Member States and the European Agency for the Evaluation of Medicinal Products. This Notice has no legal force and does not necessarily represent the final views of the Commission. In case of doubt, therefore, reference should be made to the appropriate Community Directives. It is important when reading this text to appreciate that the legal requirements of the Directives and the Regulation must be met and that this Notice presents the harmonised views of the Member States on how those requirements may be met.

The Notice to Applicants (Volume 2 in the series "The Rules governing Medicinal Products in the European Union") was first published in 1986. A revised and completed version, the second edition, was issued in January '89. Since then, the procedures for applications for a marketing authorisation have been amended in order to introduce the centralised and mutual recognition procedures. The resulting size of NTA has meant that it has been divided into parts

— Volume 2A dealing with procedures for marketing authorisation;

— Volume 2B dealing with the presentation and content of the application dossier.

Volume 2B is concerned with the structure and content of the application dossier (Parts I, II, III, IV). It provides guidance for the compilation of dossiers for applications for marketing authorization, and is applicable for the centralised procedure and national procedures, including mutual recognition. The requirements for the content of the application dossier are set out in Directive 75/318/EEC as amended, i.e. "the particulars and documents accompanying an application for marketing authorization pursuant to Article 4 of Council Directive 65/65/EEC shall be presented in four parts, in accordance with the requirements set out in the Annex to that directive, taking account of the guidance published by the Commission in *The rules governing medicinal products in the European Union*, Volume 2: *Notice to applicants for marketing authorisations for medicinal products for human use*".

The content of the dossier (Volume 2B) has not been changed since 1989 with the exception of additions in order to take account of those medicinal products brought within the scope of Directive 65/65/EEC as a result of the 'extension' directives i.e. radiopharmaceuticals, medicinal products derived from human blood and plasma and homeopathics; as well as occasional clarifications as requested by the pharmaceutical industry. In order to provide regulatory authorities and the pharmaceutical industry with a 'single source' document, the current text of the 1989 edition of the Notice to Applicants has been re-presented, with those additions and clarifications already (consulted upon and) adopted duly incorporated.

Therefore, the text of the 1989 edition is replaced by this volume.

In order to facilitate the preparation of the dossier, particularly the tabular presentations, this volume is also available on a diskette.

OVERVIEW

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INTRODUCTION

1. PRESENTATION OF THE APPLICATION

The Community application dossier, which should be submitted in either a Community or national procedure (i.e. to competent authorities of the Member States and the European Agency for the Evaluation of Medicinal Products), consists of administrative information and the necessary demonstration of quality, safety and efficacy of the product.

This is presented in four Parts (I, II, III, IV).

Part I – Summary of the dossier

Part II – Chemical/pharmaceutical/biological tests

Part III – Toxico-Pharmacological tests

Part IV – Clinical documentation.

2. PART 1

Part I is divided into 3 sub-sections:

— **Part IA** consists of the administrative data, packaging, samples, manufacturing and marketing authorisations applied for or obtained elsewhere (previously in Part V of the dossier). A harmonised format for Part IA has been agreed.

— **Part IB** consists of the proposed Summary of Product Characteristics (SPC) and package leaflet, in accordance with Article 4a of Directive 65/65/EEC. The sequence given in the guideline has been accepted by the competent authorities of all Member States, and places the clinical data in a more prominent location.

— **Part IC** consists of the Expert Reports and their Annexes.

Parts IA, IB and IC are always required. Part IB must be in the language(s) of the Member State concerned or in all Community languages for centralised applications.

2.1 Experts Reports in the application dossier

Directive 75/319/EEC as amended requires that the particulars and documents submitted in the application dossier are drawn up and signed by experts, with the necessary technical or professional qualifications. The chemical/pharmaceutical/biological, toxico-pharmacological and clinical parts of the dossier should each include an Expert Report. The Expert Reports, their tabular formats and written summaries are placed in Part IC of the dossier.

It is important to emphasise that well prepared Expert Reports greatly to facilitate the task of the competent authority in evaluating the dossier and contribute towards the speedy processing of applications. For these reasons particular care should be taken in the preparation of Expert Reports, following the guidance on the preparation of Expert Reports given in this volume.

Where relevant Community guidelines on the conduct of tests, studies and trials on a medicinal product exist, these should be taken into consideration when Expert Reports are prepared. Any deviation from guidelines should be discussed and justified. In particular, the

experts should give a justification for the statements in the proposed summary of product characteristics (SPC), taking into account the submitted data and the SPC guideline and also considering the need for bioavailability studies with reference to the guideline on bioavailability and bioequivalence in Volume III of the Rules governing medicinal products in the European Union.

2.2 Presentation of the Expert Report

Experience has shown that many applications, particularly for new active substances, have included a written summary as well as the tabulations to the Expert Reports.

Competent authorities have generally found these to be helpful. However, it is considered important to clarify the purpose of the appendices to the Expert Reports in order to avoid duplication and overlap.

It is important to avoid duplication, repetition between the Expert Report and the written summary. Equally, experience has shown that a good tabular presentation with a short written summary is an effective method of communication. Therefore, where tabular formats suffice, it is not necessary to duplicate the message in writing.

— Quality

For the quality part of the dossier, the tabular formats are considered to fulfil the function of a written summary (except in the case of biotechnology medicinal products and medicinal product which contain or consists of genetically modified organisms where a written summary of not more than 30 pages would be helpful).

The assessment report prepared by the competent authority on Part II of the dossier consists of three parts:

— annotations on the tabulated formats of the Expert Report;

— annotations on the critical part of the Expert Report (including a critical appraisal section of the Active Ingredient Manufacturers restricted part (of a DMF file);

— a critical evaluation by the assessor of key features of the dossier.

When the assessment report is to serve as the basis of mutual recognition, the applicant will be invited to provide a revised and updated version of the critical discussion and the tabulated formats of the Expert Report, based on an updated Part II of the dossier. These revisions would take into account all of the points raised during the assessment. It is these revised and updated documents which will form the basis of the (updated) assessment report referred to in Article 9.3 of Directive 75/319/EEC as amended.

— Safety

For the toxicological section of the dossier, the tabular formats are considered to fulfil the function of a written summary.

For the pharmacological section of Part III of the dossier, a written summary could be useful. Normally, the written summary would not be more than 10 pages.

It is considered helpful to have an overview table which would precede a written summary. This overview table would form part of the assessment report.

The assessment report would include a critical analysis of the Part III Expert Report, tabular formats, overview table, written summary, in the light of knowledge of the detail of the submitted dossier of study reports.

— Efficacy

A written summary can be helpful for large, complex clinical documentation. In order to aid clarity, an overview table of clinical studies should precede the written summary.

This overview table would form part of the assessment report.

The written summary should be factual, complete (i.e. covering all studies) and concise.

Normally, it would not be longer than 30 pages. However, in cases of complex dossiers, with multiple indications and/or large numbers of patients evaluable for safety and efficacy, a larger summary (up to 100 pages) could be necessary.

3. TECHNICAL DOCUMENTATION

Parts II, III, and IV of the application dossier consist of the chemical, pharmaceutical and biological documentation; the toxicological and pharmacological documentation; and the clinical documentation respectively.

In Part IV, Clinical Documentation, case report forms are always required to be available.

Although it is not necessary to include these in the submission, applicants should be prepared to supply them normally within 48 hours of any request by the competent authority and in any event within 7 calendar days of the request.

This applies (for submission of case report forms) also to the time during the evaluation procedure unless a significant change of the SPC arises from single case reports.

3.1 Overview tables

Given the pivotal role of the overview tables for Parts III and IV, applicants are strongly urged to include these in submissions, as quickly as possible. In any event, consideration of a dossier in any of the Community procedures would be greatly facilitated by the presence of such overview tables.

A written summary, for the relevant sections of Part III and Part IV would facilitate mutual recognition by concerned Member States, and also consideration by the members of the Scientific Committee of the European Agency for the Evaluation of Medicinal Products.