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## CTD GUIDELINE IRD-KLVZ-02

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Volume 2B

Notice to Applicants

Medicinal products for human use

Common Technical Document (CTD) Presentation and format of the dossier

Foreword

This Notice to Applicants (NtA) for medicinal products for human use has been prepared in order to fulfil the obligations of Annex I of the Regulation on Licensing of Medicinal Products for Human Use.

The NtA is currently published as the following volumes:

Volume 2A dealing with licensing procedures

Volume 2B dealing with the presentation and format of the dossier

Volume 2C dealing with licensing guidelines

All updates of the volumes mentioned above can be found on the pharmaceutical unit website of the European Commission at the following address:

[https://ec.europa.eu/health/documents/eudralex/vol-2\\_en](https://ec.europa.eu/health/documents/eudralex/vol-2_en)

Introduction

Volume 2B, which relates to the presentation of the dossier, provides guidance on how the files prepared for licensing applications should be compiled. In preparing this guideline, the relevant guidelines have been taken into account (for example, on the ICH website: <http://www.ich.org> and the documents published on the European Commission website).

Volume 2B CTD, which is the update of the Notice to Applicants, contains the revised ICH CTD guideline with respect to Quality, Safety and Efficacy aspects (see <http://ich.org>).

A list of CPMP/ICH guidelines related to each module has been attached and must be taken into consideration in the preparation of the licensing dossier. These will be updated at regular intervals.

The CTD is an internationally agreed format for the planned presentation of applications to be submitted to the licensing authorities in the three ICH regions: Europe, the USA and Japan. The objective of the CTD is to save time and resources and to facilitate licensing reviews and communication.

The CTD provides an appropriate format for the data obtained. Applicants should not alter the general structure of the Common Technical Document, as set out in the guideline. However, in the non-clinical and clinical overviews, applicants may modify individual formats where necessary in order to provide the best possible tabular presentation of technical information to facilitate the understanding and evaluation of the results.

The CTD format will be applicable to all application types (new chemical active substances, radiopharmaceuticals, vaccines, herbal products, etc.). Applicants need to consult the Agency in order to determine the applicability of this format to a specific product type.

Terminology

Since the Common Technical Document is an international document, European legal terms such as "active substance", "medicinal product" and "marketing authorisation" have not been used in developing the document. Applicants are reminded that the term "medicinal product for human use" covers both pharmaceutical and biological medicinal products. Unless otherwise specified, this term should be used synonymously with "product". Similarly, the term "active substance" should be used synonymously with the term "drug substance".

Terms used in ICH documents may be used in the CTD part of the application.

Submission of Licensing Applications:

The current requirements relating to the content of the dossier must be presented in accordance with Article 8 and Annex I of the Regulation on Licensing of Medicinal Products for Human Use.

Applicants are advised to consult the official internet addresses given below in order to verify the latest updated information:

For the most recently updated information, applicants should consult:

Reformatting of dossiers of medicinal products previously authorised

There is no obligation to reformat the dossiers of medicinal products previously licensed in the new CTD format. If the marketing authorisation holder wishes to reformat its dossier, this will be permitted; however, it is not recommended that this be done in the non-clinical and clinical parts of the dossier. Nevertheless, particularly after 1 July 2007, in order to facilitate the handling of variations and new forms of a product, it is recommended that companies voluntarily reformat the Quality-related part of the documentation in accordance with the CTD format. This reformatting should include the entire Quality-related sections, including and integrating any Active Substance Master File (if available) as well as all approved variations. A written statement provided by the Marketing Authorisation Holder should also be submitted, indicating that the content/data of the Quality Module is exactly the same as the approved Quality section and that no change has occurred in the dossier as a result of the reformatting. The reformatted Quality documentation presented in CTD format must include a new Module 3 in CTD format; however, it is not mandatory for it to include the Quality Overall Summary, together with a signed template for the Quality Expert. The submission of Module 1 is not required. If the original Section II contains data related to bioequivalence, these data must be taken from Section II, reformatted according to the new CTD structure and submitted annexed in a separate file. The reformatted documentation should preferably be submitted simultaneously with, but separately from, a variation, the presentation of the product in different dosages and forms (variation), or a renewal. Where necessary, a clear distinction must be made between the reformatted (unchanged) information and the documentation supporting the variation/variation or renewal submitted at the same time. Since the reformatting of a dossier does not involve any change in the content of the dossier, it does not fall under the definition of a variation from a legal perspective.

The Agency decides whether a fee will be charged. Submission of the application

The Common Technical Document is organized into five modules.

Administrative, national information is given in Module 1. This module contains the national requirements in terms of administrative data (Application Form, Summary of Product Characteristics, Package Leaflet and Labelling, etc.).

Module 2 contains high-level summaries that must be prepared by persons (experts) with appropriate qualifications and experience (Quality Overall Summary, Nonclinical Overview/Summaries and Clinical Overview/Summaries). For legal reasons, although the term "Expert Report" must be used, the content is expected to be provided in the Quality Overall Summary, Nonclinical Overview/Summary and Clinical Overview/Summary documents. Module 2 now takes the place of the former Expert Reports. Experts must provide brief information in the section on information about the experts in Module 1.4 regarding their training and specific expertise, and must sign it.

Module 3 presents chemical, pharmaceutical and biological documentation. This information must be structured as specified in Guideline M4Q.

Documentation on Toxicological and Pharmacological Tests performed on the drug/active substance and a drug/medicinal product must be provided in the Nonclinical Summaries (from Module 2) and by the Nonclinical Study Reports (Module 4). These reports must be presented in the manner specified in Guideline M4S.

Documentation on Clinical Trials conducted in relation to the drug/medicinal product can be obtained from the Clinical Summaries (from Module 2) and the Clinical Trial Reports (Module 5). These reports must be presented in the manner specified in Guideline M4E.

Schematic Representation of the Organization of the CTD

Module 2

Module 1 Not part of the CTD

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Administrative

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Preparation and Organization of the CTD

In all stages of the CTD, the presentation of the information must be clear and transparent in order to facilitate the review of the core data and to enable the reviewer to quickly navigate to the application contents. Texts and tables must be prepared using margins such that the document can be printed on A4 paper. The left margin must be sufficiently wide so as to prevent the information from becoming invisible when the document is filed. Font sizes for text and tables must be of a type and size that can be easily read even after photocopying. Times New Roman 12 point font is recommended for text. Abbreviations and short names must be defined on first use in each module.

Page Numbering and Grouping

Each document must be prepared in line with the CHMP/ICH/2887/99 Revision 1 CTD Organisation recommendation.

Specific Guidance for Different Application Types

Although this format requires certain adaptations for specific application/medicinal product types, it is intended for applications for all categories of preparations/medicinal products (new chemical substances, radiopharmaceuticals, vaccines, herbals, etc.) and all application types (stand-alone, generics, biosimilars, etc.).

The format in question is intended to show how the information included in the application should be appropriately organized, not to indicate which trials are required for a successful approval. If no information is available under a specific heading or it is not required, that part of the application must be marked as "not applicable" or "not relevant", while the section heading and, where necessary, a justification for the absence of the trial must be provided in the Quality Overall Summary, Nonclinical Overview and Clinical Overview.

For applications for well-established medicinal use (bibliographic), generic, biosimilar, hybrid and variations (presentation of the product in different dosages and forms), the Nonclinical/clinical overviews/summaries must focus on application-specific topics. Applicants must also take into account Volume 2A Licensing Procedures of the Rules Governing Medicinal Products in the

European Union.

For generic, biosimilar and hybrid applications and for variations (presentations of the product in different dosages and forms), cross-references to previous applications submitted in the "old" format will be accepted. Re-formatting into the CTD format of "old" documentation that has already been evaluated and authorized is not required.

### **1. Well-established medicinal use (bibliographic) applications**

In applications made pursuant to subparagraph 2 of paragraph (a) of the first paragraph of Article 9 of the Regulation on Licensing of Medicinal Products for Human Use, the Nonclinical/clinical overviews/summaries must demonstrate that the component(s) of the medicinal product has/have a well-established medicinal use with an acceptable level of safety or efficacy as given in Annex I of the said Regulation.

Tabulated clinical or nonclinical summaries must be provided in Module 2. Tables may not be necessary for substances with a long-standing and well-known period of use, but an appropriate justification will be required for this. The Overviews must always be included.

### **2. Informed consent, generic, hybrid or biosimilar applications**

2a) Consent of the reference marketing authorisation holder;

Applications made pursuant to subparagraph 1 of paragraph (a) of Article 9 of the Regulation on Licensing of Medicinal Products for Human Use may refer to the expert reports contained in the reference medicinal product dossier or to documentation containing quality/non-clinical/clinical overviews/summaries, provided that the marketing authorisation holder of the reference medicinal product gives its consent.

2b) Applications concerning generic, hybrid medicinal products and biosimilar medicinal products;

Applications made pursuant to subparagraph 4 of paragraph (a) of Article 9 of the Regulation on Licensing of Medicinal Products for Human Use, and to paragraphs (b) and (c) of the first paragraph of Article 9 of the same Regulation, shall include Module 2 Quality Overall Summary, Non-Clinical Overview and Clinical Overview. Non-clinical and Clinical Summaries may be provided, but they are mandatory only if additional new studies are included in the documentation.

### **3. Variation Applications Made Under the Regulation on Variations to Marketing Authorisations of Licensed Medicinal Products for Human Use**

After 1 January 2007, all variation applications must be submitted using the CTD format. However, cross-references to "old" format documentation will be acceptable, because the content is the same. Explicit references to any "old" format are required.

Examples:

- Any new (additional or revised) data supporting the variation must be presented using the CTD format.

- Where any unchanged data needs to be submitted, for example, in cases where a copy of the approved particulars may need to be submitted in accordance with the Guideline on Variations to Marketing Authorisations of Licensed Medicinal Products for Human Use, the marketing authorisation holder should subsequently update these particulars to the new CTD format. The marketing authorisation holder should provide a declaration that any reformatted document is unchanged, so that it will be able to use these "updated" (CTD) particulars for any future variation application.

If a cross-reference is made only to an approved datum, a cross-reference may be made (by Section and part) even if the file containing the datum is in the "old" format. If the marketing authorisation holder wishes to present the (unchanged) datum in the new CTD format, such an application will also be acceptable, as this will facilitate the handling of future variations. However, the marketing authorisation holder must provide a declaration that the reformatted document is unchanged.

Type IA/IB and Type II Variation Applications and their supporting documentation – where applicable – should be presented in accordance with the Guideline on Variations to Marketing Authorisations of Licensed Medicinal Products for Human Use.

#### 4. Variation Applications Made Under the Regulation on Variations to Marketing Authorisations of Licensed Medicinal Products for Human Use

Non-clinical/clinical overviews/summaries should focus in particular on the following elements:

- An evaluation of the results of studies conducted in addition to the studies on the licensed medicinal product for human use. The results should be discussed in the perspective of what is known from the published literature and previous submissions. Additional studies should be presented in the table formats given in this Notification to Applicants.
- Currently published literature relevant to the substance concerned and to the variation application should be submitted. The documentation may include annotated articles published in peer-reviewed journals acceptable for use for this purpose.
- Any claim in the Summary of Product Characteristics (SmPC) that is known or derived from particulars of the medicinal product for human use or the therapeutic class concerned should be discussed in the non-clinical/clinical overviews/summaries and substantiated by published literature or additional studies.

As of 1 July 2007, variation applications for the product must be presented using the CTD format. However, reference may be made to the "old" sections of the dossier that have previously been evaluated and licensed; such references may be made only where no additional data are submitted for those sections. In such cases, it is not mandatory to reformat the previously evaluated and licensed "old" documentation.

Module 1 and 2 must always be submitted. Where no new clinical or non-clinical data are submitted, expert reports may replace the relevant overviews/summaries. However, it is mandatory to submit a summary and overview section in the new CTD format covering the new information or data submitted to support the application. All headings (numbers and titles) must be included in this summary/overall summary in CTD format; however, where a cross-reference can be made, since the data are unchanged, a statement such as "Not applicable — unchanged" (or similar) must be included.

In addition to presenting the quality data concerning variation applications for new presentation forms of the product in CTD format, marketing authorisation holders are recommended to completely reformat "old format" Section II, which has been evaluated and licensed, in order to obtain a comprehensive CTD Module 3 covering all strengths/pharmaceutical forms. By way of exception, in the case of multiple strengths and/or pharmaceutical forms, the Quality module of the variation of the medicinal product for human use may include only the data related to the new strength/pharmaceutical form and may cross-refer to the relevant "old" quality data. Where a subsequent variation affects the "old" section, marketing authorisation holders are required to (at least) reformat the relevant section in CTD format.

#### **4. Renewal Applications:**

As of 1 January 2007, all applications made for renewal must be submitted using the CTD format. The guidance set out in the relevant guidelines/recommendations on the handling of renewals should be taken into account. See Volume 2C, <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev2.htm>

Specific guidance on herbal medicinal products

Within the framework of this document, the terms "herbal substances and preparations" should be considered equivalent to the terms "herbal drugs and herbal drug preparations" as defined in the European Pharmacopoeia.

For ease of reference, the section headings in Modules 2 and 3 have been copied. The texts under the section headings are only explanations and descriptions relating to herbal medicinal

products. The content of these sections should include the relevant information described in the Guideline published by the Agency.

See here for specific information on herbal medicinal products:

- Module 2
- Module 3

Active Substance Master File (ASMF)

The existing guideline on the ASMF procedure (CHMP QWP/227/02) 3 applies in principle; that is, the responsibility of the applicant applying for a marketing authorisation for a medicinal product for human use is to ensure that the entire ASMF — in other words, both the applicant's "open" part and the "closed" part of the active substance manufacturer — is submitted directly to the competent authorities by the active substance manufacturer in CTD format and arrives at the same time as the marketing authorisation application. A copy of the "Letter of Access" must be included in Module 1, in the Application Form as Annex 6.10, and must be addressed to the competent authority to which the application is submitted.

The part of the ASMF that is "open" to the applicant must be included in section 3.2.S of the quality documentation presented in CTD format.

In the ASMF, the "closed" part of the active substance manufacturer must follow the structure of Module 3.2.S of the CTD. For the information included in the "closed" part of the active substance manufacturer, the Overall Quality Summary must also be presented as part of the ASMF.

When a new ASMF application is made in CTD format as part of the quality data, the entire ASMF (the open and closed parts of the ASMF and the Overall Quality Summary) must be presented in CTD format.

3 Guideline on the Active Substance Master File procedure for the previous European Drug Master File (EDMF), CPMP/QWP/227/02

<http://www.emea.eu.int/htms/human/qwp/qwpdraft.htm>

Variations to the ASMF:

If a change has been made to any part of the ASMF, the documentation relating to that change must be presented in CTD format. In this process, it is recommended that the ASMF holder reformat the entire ASMF. This will facilitate the handling of changes/variations affecting the data in the relevant ASMF.

The ASMF holder must make a clear distinction between the following: - The reformatting of ASMF data previously assessed by the Agency, - New documentation supporting the change in the ASMF data.

If an ASMF has been reformatted into CTD format without any change in the data, a signed statement must be submitted by the ASMF holder guaranteeing that the content of that ASMF is identical to the current version of the ASMF.

After the ASMF has been reformatted, the new "open" part of the ASMF in CTD format must be sent by the ASMF holder to the relevant marketing authorisation holder, so as to enable the marketing authorisation holder to update all marketing authorisations for which the relevant ASMF has been used. The presentation of the ASMF in CTD format will be accepted without any need to reformat the relevant quality data in the dossier of the medicinal product for human use.

In the event of a change in the ASMF data, the relevant variation must be submitted to the authorities by the marketing authorisation holder. For marketing authorisations in which an ASMF is used, in variation applications made for the authorised product, the ASMF holder must reformat the entire ASMF into CTD format and thereby ensure that the "new" ASMF format is included in the variation application for the product, rather than cross-referencing the "old" ASMF format.

Monographs relating to the Certificate of Suitability of the European Pharmacopoeia (CEP)

Applicants may use the CEP scheme in place of some of the information required in Module 3 for active substances described in the European Pharmacopoeia.

The Active Substance section must refer to the Certificate of Suitability in the relevant sections of Module 3.2.S. As Certificates of Suitability are assessed to replace the relevant sections, no additional information will be needed except for technical product characteristics not covered by the Certificate of Suitability (e.g. the Certificate of Suitability does not describe a specific technical grade).

A comprehensive copy of the Certificates of Suitability (including annexes) must be presented in Module 1 and Module 3 R, and in Annex 6.10 of the Application Form.

Compliance with BSE/TSE can also be demonstrated by means of a Certificate of Suitability.

European Community Guideline on Quality, Safety and Efficacy

When preparing the dossier for a marketing authorisation application, applicants must take into account the Community guideline on the quality, safety and efficacy of medicinal products published by the Commission in "The Rules Governing Medicinal Products in the European Community", Volumes 3A, 3B, 3C: Guidelines on the quality, safety and efficacy of medicinal products for human use, and subsequent updates adopted by the Committee for Proprietary Medicinal Products. Guidelines adopted in the ICH process are considered Community guidelines after being adopted and published by the CPMP. References to the relevant Community or ICH guidelines have been included in the relevant sections or in each section of the dossier. For the latest updates of the Community/ICH guidelines, applicants are advised to consult the EMEA website at <http://www.emea.eu.int/index/indexh1.htm> (Notice to Applicants — Guidelines and Guidance Documents).

In the quality-related part of the dossier, the monographs and general chapters of the European Pharmacopoeia are also applicable. All materials of ruminant origin must also comply with the requirements of the Certificate of Suitability.

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