PREPARATION OF COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE IN AUSTRALIA

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ABSTRACT
For registration of pharmaceutical products in regulated and non-regulated market common technical document (CTD) submission is important. Common Technical document is divided into 5 modules. Module-1 contains administrative information and it is country specific. Module-2 contains overviews and summaries of 3-5 modules. Module-3 -Quality information. Module-4 contains non clinical reports. Module-5: clinical study reports

Key words: *Common technical document, Module, Australia.*

INTRODUCTION
Regulatory Affairs is a comparatively new profession which has developed from the desire of governments to protect public health, by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines [1-3]. The Common Technical Document (CTD) is a set of specifications for a dossier for the registration of medicines. The CTD was developed by the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and adopted by the TGA [4, 5]. A dossier contains and/or references the necessary data to demonstrate the quality, safety and efficacy of a prescription medicine [5, 6]. A submission is a collection of one or more applications that are grouped together for fee purposes, and is specific to a particular active ingredient and applicant.

Over view of CTD

The CTD prescribes: The organization of the dossier across 5 modules [4, 7, 8]. The order in which documents must appear so they are grouped logically and can be easily located. Under the CTD format, each application is a collection of documents grouped into 5 modules as detailed below. The actual content of the dossier will vary according to the application category and application type.

The format and content of Module 1 are described in this document [4].

The format of Modules 2, 3, 4 and 5 is described in the relevant adopted CTD guidelines. The content of Modules 3, 4 and 5 (technical data requirements) will vary according to the application type and is described in the relevant Australian guidelines and adopted EU guidelines

Structure of CTD

Module 1: Administrative information and prescribing information (country specific) (AUSTRALIA) - The format of Module 1 is unique to Australia and contains relevant administrative documentation [9-11]. Part A-CTD Module-1 of the common technical document describes the administrative information and prescribing information for Australia to support an application to register a prescription medicine under section 23 of the Act & vary the details of an ARTG registration for a prescription medicine under section 9D of the Act [9, 12]. Electronic lodgement' means the applicant has created an application in e-BS and subsequently printed out an application form and an electronic lodgement cover sheet. Sequence numbers, as defined for e-CTD submissions, are not applicable for non e-CTD electronic submissions format dossiers. However, the use of a four digit number in the top level folder name is recommended. The initial application should normally have a sequence number of 0000. As additional data is submitted, for example, in response to questions, the sequence number will advance, 0001, 0002, etc.

Before a newly approved registration can be included in the ARTG, one of the following forms is required to satisfy legislative requirements under section 26B of the Act: Certification in relation to patents required in relation to registration or listing under Sections 25, 26 and 26A of the Therapeutic Goods Act 1989 [13]. Notification to the Secretary that a Certification under section 26B (1) of the Therapeutic Goods Act 1989 is not required [13, 14]. All applications for new registrations, including formulation changes, changes in trade name, and extensions of indication, require the applicant to provide one of the above forms before the registration process can be finalized.

Consumer medicines information Include in all applications which: Result in a separate and distinct good under section 16 of the Act. Relate to a variation that will result in a change to the CMI

Information about the expert Non-clinical

Include where any subsection of Module 2.4 and/or Module 2.6 has been provided in the dossier. Module 1.4.2 must include, in the following order: The expert's signed declaration, and the expert's curriculum vitae.

Specific requirements for different types of applications: This section of Module 1 holds multiple documents required for specific types of applications

Module 1.5.1 Literature-based submission documents: Include where the application partially or completely relies on a literature-based data set to support the application.

Module 1.5.1.1: Methodology of literature search, including complete details of database search strategies.

Module 1.5.1.2: A copy of the letter from the TGA in which approval for the search strategy is given.

Module 1.5.1.3: Complete search output.

Module 1.5.2: Orphan drug designation.

Include when the medicine has been designated an orphan drug and the applicant wishes to request the fees be waived for an application under section 23 of the Act.

Drug and plasma master files and certificates of suitability of monographs of the European pharmacopoeia [11, 15]: This section of Module 1 holds multiple documents relating to the use of drug

master files (DMFs), plasma master files (PMFs) and Certificates of Suitability of Monographs of the European Pharmacopoeia (CEPs) to establish the quality of active substances in the medicine, novel excipients and excipients of animal and human origin.

Relevant external sources: Include this document when the application makes reference to one or more: Drug master files (DMFs), Plasma master files (PMFs), and Certificate(s) of Suitability of Monographs of the European Pharmacopoeia (CEPs).

Good manufacturing practice: This section of CTD Module 1 holds multiple documents relating to the Good Manufacturing Practice (GMP) status of the manufacturer(s) of the new medicine or registered medicine to be modified. All manufacturers and finished product testing facilities involved in the active ingredient and/or product manufacture must have one of the following: Manufacturing license(s), GMP clearance(s), and an application lodged with the Office of Manufacturing Quality (OMQ).

GMP documentation is also required for excipients derived from human blood or plasma (for example, Albumin) and complex biotechnological excipients, the activity of which is a functional aspect of the medicine.

Applications for TGA GMP clearances:

GMP clearances to support category 1 or category 2 applications for non-biotechnology products are not available or have less than 6 month's currency at the time of dossier lodgement with the TGA. Applications have been lodged for renewed or updated GMP clearances to support category 1 or category 2 applications where GMP clearance will expire during the evaluation period [9, 15].

Details of any additional data to be submitted: The TGA will only agree to the lodgement of additional data where the medicine is of critical importance to the Australian community to address emergency or safety situations. No other data should be submitted during the evaluation of an application, other than relevant safety data and data specifically requested by the TGA.

Individual patient data: This section of the Module 1 holds information regarding the applicant's ability to provide individual patient data, should the need arise, to support the studies provided in the dossier. Include for applications where a full set of individual patient data has not been provided to the TGA and the application: Contains clinical studies, and references another dossier containing clinical studies [9]. In general, this is tabulated patient data that includes clinical and laboratory monitoring results formatted to show a relationship to individual patients. Include details of additional data to be submitted when discussions have resulted in the TGA agreeing to accept additional data during the course of evaluation.

Information relating to pharmacovigilance: This section of Module 1 holds documents relating to the pharmacovigilance activities for a new medicine, or significant changes to a registered medicine.

Include in all applications for: A new chemical entity, a similar biological medicinal product, and a generic medicinal product where a safety concern with the reference medicinal product requires additional risk minimization activities.

Unless TGA has agreed that it is not required, include a risk management plan (RMP) for applications involving: A significant new registration (for example,

new dosage form, new route of administration, significant change in indications, extension of paediatric population). A significant variation in a registration (for example, new manufacturing process of a biotechnologically-derived product).

Module 2: Common technical document summaries [4, 16-18].

Module 2 summarizes the information that will be provided in the quality (Module 3), nonclinical (Module 4) and clinical (Module 5) modules of the dossier. There is no single document that explains the content of Module 2 for the registration of pharmaceuticals for human use.

The documents for Modules 3, 4, and 5 include a section on the information that must be provided in Module 2.

- CTD for the registration of pharmaceuticals for human use Quality overall summary of Module 2 and Module 3: quality
- CTD for the registration of pharmaceuticals for human use Nonclinical overview and nonclinical summaries of Module 2 and organization of Module 4
- CTD for the registration of pharmaceuticals for human use clinical overview and clinical summary of Module 2 and Module 5: clinical study reports

Module 3: Quality [4, 16]

Module 3 describes the format and organization of the chemical, pharmaceutical and biological data relevant to the application. This module is an EU CTD document adopted in Australia. A table of contents for the field application should be provided

Body of Data which includes: Drug Substance (Name, Manufacturer), general information (name, manufacturer), and nomenclature (name, manufacturer)

Materials used in the manufacture of the drug substance should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided, as appropriate. A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and if available, production scale batches. A description of the container closure system should be provided, including the identity of materials of construction of each primary packing component, and their specifications. The specification should include description and identification. Non-Compendial methods should be included where appropriate. For non-functional secondary packing components, only a brief description should be provided. For functional secondary packing components, additional information should be provided. The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

Results of the stability studies should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical

procedure used to generate the data and validation of these procedures should be included. The pharmaceutical development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instruction are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally this section should identify and describe the formulation and process attributes that can influence batch reproducibility, product performance and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached to the pharmaceutical development section.

Module 4: Safety (Non-clinical study reports)

Module 4 describes the format and organization of the nonclinical (pharmaco-toxicological) data relevant to the application. This module is an EU CTD document adopted in Australia [4, 17].

Module 5: Efficacy (Clinical study reports)

Module 5 was describes the format and organization of the clinical data relevant to the application [20]. This module is an EU CTD document adopted in Australia. Bio analytical studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative Bio analytical or Bio equivalence studies may use pharmacokinetic, pharmacodynamic, and clinical or *in vitro* dissolution endpoints and may either single dose or multiple dose. When the primary purpose of study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in section. *In vitro* dissolution studies that provide BA information, including studies used in seeking to correlative in vitro data with in vivo correlations should be placed in section 5.3.1.3. Reports in vitro dissolution tests used for batch quality control and/or batch release should be placed in the quality section of the CTD [17, 21]. Bioanalytical and/or analytical methods for Biopharmaceutic studies or in vitro dissolution studies should ordinarily be provided in individual study reports. Human biomaterials is a term used to refer to proteins, cells, tissues and related materials derived from human source that are used in vitro or ex vivo to assess PK properties of drug substance. Examples include cultured human colonic cells that are used to assess permeability through biological membranes and transport processes and human albumin that is used to assess plasma protein binding [4, 17, 21].

Reports of Efficacy and Safety studies

This section should include reports of all clinical studies of efficacy and/or safety carried out with a drug, conducted by the sponsor, or otherwise available, included all completed and all ongoing studies of the drug in proposed and non-proposed indications. The study reports should provide the level of detail appropriate to the study and its role in the application. ICH E3 describes the contents of a full report for study contributing evidence pertinent to both safety and efficacy. Many clinical issues in an application can be addressed by an analysis considering data from more than one study [22]. The result of such an analysis should generally be summarized in the clinical summary

documents, but a detailed description and presentation of the results of such analyses are considered critical to their interpretation.

CONCLUSION

For registration of pharmaceutical products in regulated and non-regulated market CTD submission is important. Due to major difference in the regulatory requirement for registration of dossier for Pharmaceutical Product CTD format was introduced. CTD format helps to compile the documents in the defined format as mentioned above as per the requirement of the registering country The process for smooth registration of drug product becomes easier by complying all the requirements to get approval of global market at the same time and to launch the product at once in different market. So before introducing the product in any of the country one should understand the requirement.

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