An Overview and Review of Chemistry, Manufacturing, and Control sections of the CTD Dossier

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ABSTRACT:
The current article reviews and simplifies the marketing application criteria, including the crucial elements of marketing applications in various CTD-using nations. It also examines the CMC section's (Chemistry Manufacturing & Control) requirements for applying to regulated markets. The main points of attention are the submission of applications and any queries that could be made later or during the approval procedure. The study demonstrates the creation of a dossier using the CTD format with few filing mistakes. Therefore, it is essential to concentrate on the criteria for dossiers with few questions and research the likely questions that could come up after submitting an application to a country with regulations.

Keywords: CTD, CMC, Drug substance, Drug product & Queries

INTRODUCTION:

When 100 deaths from diethylene glycol poisoning were linked to the use of a sulphanilamide elixir in the USA in the 19th century, regulations in medicine were first instituted (1). About 10,000 infants with phocomelia and other birth defects were born as a result of the thalidomide tragedy in the year 1960s (2). The governments were prompted to consider enacting stricter controls for drugs as a result. Following these occurrences, other nations, particularly the USA and certain European countries, began formulating regulatory principles and restructuring their regulatory bodies (3). Representatives from the European Medicines Agency (EMA), the United States Food and Drug Administration, and the Ministry of Health, Labour and Welfare in Japan created a set of guidelines in 2000 that specified the format and information that should be included in an application for the registration of a new drug that could be used in all three countries. The International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use is in charge of implementing the standardized framework for CTDs (4). A well-structured presentation for marketing applications submitted to regulatory agencies should be prepared using the CTD format. As a single format for submitting NDA, CTD makes it easier to submit applications simultaneously in many areas (5). The primary goal of this CTD format is to harmonize the quality information, particularly Chemistry Manufacturing and Control (CMC), which is supplied in an application format. CTD comprises five modules; Mod – 1: Administrative information & prescribing information, Mod – 2: CTD summaries, Mod – 3: Quality, Mod – 4: Non-clinical study reports, and Mod – 5: Clinical study reports. The ICH M4 standards describe the general organization of the CTD in depth. They also contain a granularity section that offers instructions on where to place documents and how many pages to use in the CTD dossier. This information on granularity is beneficial if the dossier comprises several indications or several of the investigational medicinal product's components. (IMP). A list of questions and answers is also supplied in addition to the M4 guidelines to address the most typical concerns. (M4)

COMMON TECHNICAL DOCUMENT:

Only pertinent information should be included in a CTD format. If the applicant considers it necessary to contribute it to support his application, any extra material not contained in CTD may be added. Times New Roman font with a 12-point size is supplied. CTD needs to be written like a story. After each Module, references should be referenced systematically (6) (7).

Module 1:

Module 1 doesn't technically belong in the CTD because it contains papers unique to each region, including application forms or the suggested label. As the content and structure of this Module vary among different Regulatory Authorities, it won't be covered in any further depth in this article (8).

The WHO's Bioequivalence Trial Information Form (BTIF) specifies that a summary of the bioequivalence/bioavailability data should be included. To submit a quality information summary (QIS), follow the guidelines in the WHO's Guideline on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product (FPP): Quality Part (9).

Module 1 summarizes information about regional administration, including a cover letter, a table of contents, an application form, information about the product, clinical and non-clinical data, pharmacovigilance work, a certificate and documents for the drug, including a GMP certificate, and a certificate of analysis of the drug substance with suitability, as well as patent information. Price lists and other associated materials, then follow the information on medicine pricing.

Module 2:

The summaries of the documents needed for the approval of the medicine are included in Module 2, Common Technical Documents, which is also where they are summarized. This Module contains general details on drug substances, their production, management, and information on the drug's reference standards. The technical document also includes information on the medicine's stability, the product form it has generated, a description of it, a list of all the ingredients, and drug reference standards. Novel percipients, regional information, and an overview of clinical and non-clinical information are also included in Module 2. As it comprises information on the biopharmaceutics of the drug, clinical pharmacology, effectiveness, and safety, this Module is crucial for the CTD structure. It is also required to summarize the pharmacodynamics and pharmacokinetics of the drug in the body. The body's distribution, metabolism, and excretion of the drug are all considered in drug analysis techniques. Also, this Module specifies the drug's single-dose and repeated-dose toxicity. Another crucial element is drug tolerance. Finally, this Module discusses an overview of biopharmaceutics, related analytical techniques, summary findings, and clinical effectiveness. Also, a description of clinical safety variables influencing the medication that may be intrinsic or extrinsic information on whether the drug may be taken during pregnancy and breastfeeding, information on drug overdose, and post-marketing data are included.

Module 3:

The drug's quality is covered in Module 3. This Module covers the drug's quality as well as its complete data. It includes facts on the material used to make the medicine, including its name, structure, and grades. It also provides information about how the chemical was manufactured and how the procedures were managed. The characterization of the medicine is covered in this section as well. It also contains information on the drug's specifications. Although this Module focuses on medication quality, it also keeps track of material reference standards and stability data. Together with the description and content of the medication product, quality also evaluates the medicine itself. Creating new formulations and developing new pharmaceuticals both contributed. The compatibility of the drug with the body is another aspect of quality. After that, it includes production and batch formula data and a manufacturing, validation, and assessment description. The analytical processes used to create the medicine are included in this Module's last section, along with a justification and a list of requirements. When the optimum stability is examined after quality is reviewed, the contaminants and their features are also discussed (10).

Module 4:

Multisource goods are generally irrelevant (but there may be occasional exceptions) (9).

Module 5:

According to its findings which also contain reports on biopharmaceutics studies and bioavailability of research reports, Module 5 identifies or communicates the specifics of all clinical investigations. Also, it includes the in-vivo and in-vitro correlation of the clinical trial findings with the bioanalytical technique reports. The report on biopharmaceutics, pharmacokinetics, and pharmacodynamics studies that ensure that the drug product is safe and effective to use will be done under this Module, which is the Clinical portion. The report also includes an individual patient's case report form (11).

DRUG SUBSTANCE AND DRUG PRODUCT

General information:

- Nomenclature – Consists of Chemical name, laboratory code & CAS registry number
- Structure – Comprises Molecular formula & molecular weight
- General properties – Description, solubility, therapeutic category, hygroscopicity, melting range, pKa values, partition coefficient & polymorphism are described in detail (12).

Manufacturing process and process control:

- Information on the production formula in detail.
- Details of the synthesis and purification processes for API are mentioned.
- The requirements for the reagents, catalysts, starting materials, intermediates, and solvents employed in the reaction.
- Equipment kind, size, and capacity.
- Details of process testing and control
- The batch manufacturing record and the master formula are mentioned.
- Reports of three batches with the same size and identical composition—the protocol for process validation—are submitted (13).

Control of materials:

- The usage of each item during the production process should be listed in a comprehensive list of the materials utilized.
- It should be stated how these materials are controlled and of what grade.

Control of critical steps and Intermediates:

- The supplier's and internal certificates of analysis should be added to the control of materials.
- It mentions a flowchart of crucial phases and process control.
- Specifying environmental factors like temperature, humidity, and airflow range is important (12).

Process validation and evaluation:

- Process validation must be done to examine the findings, analysis, and conclusions of the conducted batches. The whole batch studies concerning the manufacturing process, essential parameters, and batch size must be conducted during process validation. When choosing critical process controls and limits, it is vital to cross-reference or give evidence of the validation of the related assay and analytical procedures (13).

Manufacturing Process Development:

- The creation of the manufacturing process is required for drug substance batches created during research and development, including batch number, manufacturing scale, and application (such as stability). The ability of the manufacturing process to affect the quality of the drug substance

(and intermediate, as necessary) must be considered while assessing it. A discussion of the data should be provided, along with an explanation of why the Test was chosen and an evaluation of the outcomes. Non-clinical and clinical studies from other submission modules utilized to evaluate the effects of the manufacturing process on the drug substance(s) and related drug product(s) should be included (12).

Elucidation of the structure and other characteristics:

- Appropriate scientific evidence should support the Polymorphism & Identification of Stereochemistry of the Active Ingredient among other spectrum investigations. (Take IR, UV, NMR, Mass, DSC, XRD, etc.) Included should be the XRD test report.
- It is detailed how spectrum data from instruments like NMR, X-ray diffraction, elemental analysis, and IR may be used to show the chemical structure of substances (12).

Formulation development:

- Critical raw ingredients from two distinct vendors manufacture the finished product. However, differences in the final product's quality have not received any special attention.
- The notion of QbD should be considered when preparing the development report.
- Process control information such as moisture (range), blend homogeneity, bulk and tapped densities, and particle size distribution should be provided.
- It will be necessary to create dissolution techniques and research the impact of particle size (13).

Overages:

- Details on the API assay potency calculation formula are given (13).

Impurities:

- Data limited by API impurity (COA)
- Verify the ICH criteria.
- Verify any pharmacopoeia restrictions.
- Information on API stability.
- Data on the stability of finished products, etc.
- In addition to the typical process impurities, residual solvents, and degradation impurities, starting material impurities, elemental impurities, nitrosamine impurities, azido impurities, etc., should be under the ICH/Pharmacopoeias limit.
- The final product's specification must accurately account for the contaminants.
- It should be possible to profile the impurities in the product from each source.
- The impurity profile should include a description of any potential contaminants.
- Methods of measurement for the impurities should be given.
- Hazardous chemicals and toxic inorganic compounds should have residual limitations specified when used in a reaction during synthesis.
- To establish the Limit of Specified Impurities in the Medication Product Specification, RLD/RS/Innovator to expiration testing is helpful.
- The API should have unknown contaminants within ICH limits or less (14)(15).

Analytical procedures:

- The specification page of the DMF should have a reference to the method.
- The GC and HPLC procedures used to regulate residual solvents and contaminants in the drug ingredient should be given with the Limit of Quantification (LOQ) and the Limit of Detection (LOD).

- There should be specific GLC/HPLC procedures that have been verified to classify the contaminants. A report on TLC should be supplied.
- The results of the validation tests conducted in the MOH laboratory are ambiguous.
- As indicated, the approved technique must match the final method used to test the drug material.
- For a specific batch of the API, typical chromatograms must be provided.
- In many nations, the protocol, the report of the validation of the analytical method, and their chromatograms are required documents.
- If necessary, the agency must check the non-compendia approach verification.
- To allow for the application of more significant limitations for shelf-life, the assay limits at release should be altered and restricted to 95-105% (16).

Batch analysis:

- It is necessary to produce a report on the first three batches of API manufacturing.
- The nations' regulatory requirements should be considered while choosing a batch (ICH requires a COA report).
- The batch size should be indicated on the COAs (certificates of analysis) with other customary information.
- Working and secondary standards should come with a Certificate of Analysis (COA) (13)

Excipients:

- Excipients of natural origin should have established microbial limits.
- The manufacturer's TSE/BSE certificates have to be included.
- For adventitious agents, offering information on topics like Asbestos in Talc is necessary.
- Colors and flavors must be permitted and authorized.
- Excipients from non-compendia are not advised. Pharmacopoeia permits the use of standard combinations that contain excipients. In these situations, the supplier has to be given a table outlining the composition of the mixes in question and the standards and test form.
- A copy of the book and copies of the procedures mentioned in the monograph but not included therein should be given, along with specific excipient information.
- It should be clear what additional requirements there are beyond the monograph.
- (For instance, solvent remnants and particle size)
- Excipients An analysis certificate was tested in accordance with all requirements.
- A quantitative assessment of excipients should be used to demonstrate equality between the Test and the innovator (17).

Finished Product Specification:

- The analysis should be done using the WHO and ICH Q6 techniques (18).

Reference standards or materials:

- Requirement: Reference standards or testing materials should be presented with high-quality data tabularly (12).

Container Closure System:

- The moisture permeation statistics for the suggested blister pack should be given.
- A study on the extractable and leachable properties of plastic stoppers and containers used in the packaging of pharmaceutical products is mentioned.

- A change in the blister design and the inclusion of an ADR Reporting Statement in the unit carton box and package insert were both indicated in the labeling materials (actual/commercial label).
- A test for aluminium identification and a test for the PVD coating's infrared reflectance should have been part of the principal packaging specifications. A PVC coating IR spectrum was also needed, which you had to deliver (19).

Packing material:

- The packaging material must be compatible and suitable for storage and transport.
- For primary packaging materials, precise requirements, analysis methods, and construction material identification are needed.
- Specifications and analytic techniques are necessary for secondary packaging material.
- Printed packaging, PIL samples, and colored artwork A batch packaging record and certificate of analysis are required.
- The Polybags' IR spectra ought to be provided. (Description of the building's composition).
- The polymer must be tested, identified, and characterized per Pharmacopeia's General Monographs to be employed as an immediate container for the API product (13).

Product stability:

- A product's stability, compliance with completed product standards throughout its intended shelf life, lack of significant production of harmful breakdown products during this time, preservation of potency, efficacy, etc., must all be proven by evidence.

Stability Summary and Conclusion:

- All requirements under the ICH Guidelines are acceptable except for real-time storage conditions, which should be 30°C and 75% RH.
- It's important to think about providing moisture protection for the packing.

Stability data:

- A suitable format (tabular, graphical, or narrative) should communicate the stable study results. It should contain details on the analytical techniques employed to produce the data and how these techniques were validated (12).

Pharmacological and Toxicological data:

- The dossier includes published references for toxicological and pharmacological studies.
- The dossier includes references and published data on clinical trials.
- It is recommended to supply SmPC and clinical data from RA agency websites (20).

Bioequivalence:

- Evaluates the difference between the systemic exposure profile of a reference product and a test product (Generic) (Innovator Brand)
- The test product must absorb similarly to the reference product in terms of both rate and extent for it to be considered bioequivalent.
- For tablets, capsules, and oral suspensions, among other products.
- It may be waived in the case of aqueous oral, parenteral, or locally applied and locally acting solutions, such as eye drops, topical applications, inhalators, or nasal sprays.
- If a bioequivalence study is unavailable, information on the product's comparative dissolution profile with an innovator product should be supplied in a multimedia, multipoint format. Data must meet the requirements for the F2 factor.
- CDP should be given access to all three media and any other media (if there) (21).

Registration fees:

- In accordance with the import country's agency rules, registration costs must be paid.

Other requirements:

- Working Standards and an analysis certificate are also provided.
- Examples of APIs, working standards, columns, and more.
- Where relevant, chromatograms and spectra of the identification tests.

Samples:

Fresh samples of the finished product must be submitted with the dossier following the required quality. The sample size varies depending on the importing country's agency's requirements for registration. When samples arrive at MOH, they should typically be within a year after expiration (13).

QUERIES IN A DOSSIER:

ACTIVE PHARMACEUTICAL INGREDIENT

1. When an API exists in different polymorphic forms, then the following requirements should be included,

- ✓ Propose the appropriate method(s) for testing of polymorphic form
- ✓ Please demonstrate that the technique used to test the polymorphic identity is capable of distinguishing different polymorphs
- ✓ Include study results to verify that the same polymorph is produced consistently by submission of not less than three API batches which are consecutively manufactured
- ✓ Confirm the polymorph of API lot(s) used to manufacture the bio-batch
- ✓ Please discuss the stability of the polymorph obtained during manufacture and throughout storage
- ✓ The omission of a test for the polymorphic identity in the final API specifications from the FPP manufacturer should be discussed and justified.

2. Provide information on the solubility of the API expressed in mg/ml for your API in 250 ml water content at pH 1.2, 4.5 & 6.8 performed at 37°C. In addition, please commit to including the information in section 3.2.S.1.3 of future versions of your Drug Master File.

3. If the API is a BCS Class II molecule, it exhibits low solubility; therefore, particle size distribution (PSD) is a critical quality attribute (CQA). In this regard, please provide data on studies done to identify the PSD of the API lot used to manufacture bio-batch. Consequently, limits using laser diffraction should be set and included in the API specifications from the FPP manufacturer. In addition, submit the certificate of analysis of API bio lot included with results of PSD.

4. Analytical methods developed from Pharmacopoeia monographs should be confirmed for applicability. Therefore, you are requested to provide data on analytical method verification for the compendia methods used to determine assay and related substances for the respective active ingredient. And also provide data on AMV for the In-house techniques used to determine residual solvents.

5. If the active ingredient used in the manufacturing process of your API is a potential impurity, then you are requested to include skip testing in the API specifications from the FPP manufacturer. Your response should include submitting revised, signed, dated, and version-numbered API specifications and analytical methods with change history.

6. If it is mentioned that the information related to the control of API is in the closed part of APIMF, then you are advised that the restricted part of DMF can be submitted directly by the API manufacturer to the respective regulatory authority. Note that the copies of the API-DMF which should include the following information:

i. Both the narrative and schematic synthetic route of the API should have a description of the manufacturing process and process controls, control of materials control of critical steps and intermediates, process validation, and manufacturing process development of the APIs;

ii. Information on the characterization of impurities should include the following:

- ✓ Identification of potential and actual impurities that may arise from the route of synthesis, including those listed in the British Pharmacopoeia;
- ✓ The basis for setting the acceptance criteria for impurities
- ✓ Data on observed impurities from relevant batches
- ✓ Justification of the proposed acceptance criteria for the impurities

7. Revise the specifications for the primary component of the container closure system to include an appropriate test for identification. Submit at least one signed and dated certificate of analysis for each element of the CCS. Your submission should contain signed, dated, version-controlled specifications and analytical methods for the CCS.

8. The justification for not submitting the requested validation and verification data was unacceptable. You should have provided data on the validation of the method for estimating residual solvents in the active ingredient by the FPP manufacturer.

9. In reference to standards or materials, overlaid IR spectra comparing the primary and working standards should be provided. Also, provide the certificate of analysis for the primary and working standards.

10. When no hold times are declared for intermediates and bulk products in the manufacturing practice, you must declare any hold time periods during the manufacturing process. Note that hold time data should support a hold time period of more than 30 days and/or cumulative hold time of more than 90 days.

11. If the re-test period for the active ingredient was stated to be respective months. In addition, you must provide stability protocol and stability results, which were the basis for assigning the re-test period at the respective API manufacturing sites.

12. Should provide a commitment to place at least one batch on stability trial annually.

13. Submit signed and dated API specifications from the FPP manufacturer. The specifications should bear reference and version numbers. In addition, submit the certificate of analysis of the active pharmaceutical ingredient batches from the FPP manufacturer.

14. Submit at least two signed and dated certificates of analysis of the API from the FPP manufacturer.

15. If applicable, submit the names and addresses of the two API manufacturing sites, including the unit or block number (22).

FINISHED PHARMACEUTICAL PRODUCT

1. It was noted that overages are noted for the active ingredient. You are required to state the reason for the addition of certain overages to the formulation.

2. You must provide a justification for including the preservative in a tablet dosage formulation.

3. In case there is an excipient known to be a safety concern for some patients, you are required to update the product information documents to include the warnings accordingly.

4. The information provided regarding formulation development has been considered incomplete. You are therefore required to submit complete information on pharmaceutical development that should include, at a minimum;

- ✓ Definition of the quality target product profile (QTPP) as it relates to the quality profile of the formulation and identification of the FPP's potential critical quality attributes (CQAs) to adequately control the product characteristics that could have an impact on quality.
- ✓ Discussion of the potential CQAs of the API(s) which might affect the FPP quality
- ✓ Characterization of the innovator product against your product concerning assay, Dissolution, impurity profile, and microbiological properties.
- ✓ Further, it appears that commercial formulation and the chosen manufacturing process were not optimized through incremental changes in the concentrations of the excipients such as glidant, lubricant, disintegrant, and diluent.

Alternatively, you may submit a product quality review in lieu of formulation development. Note that the product quality review report should include all the batches manufactured during the previous one-year period, with at least ten batches or 25 batches over the last three previous years.

5. If you have included certain overages in formulation to compensate for loss during the manufacturing process, you are requested to provide data/information showing which steps of the loss occur, reasons for the failure, and measures taken to reduce the loss. You are also required to provide results for at least three batches of the finished product with and without overage to justify the loss. You may be asked to revise your master production documents.

6. If the antimicrobial study was performed, you were required to submit the antimicrobial preservatives study report since antimicrobial preservatives were included in this formulation. The amount used should have been justified by the submission of results of the product formulated with different concentrations of the preservatives to demonstrate the least necessary but still effective concentration. Should provide supportive data on studies conducted.

7. Batch numbers used for the product in process validation were not consecutive. Please explain the consecutiveness nature of these batches and provide a batch numbering SOP supporting your response. If the studied validation batches were not consecutive, you are requested to provide a process validation protocol for the prospective validation of three consecutive batches. In addition, you are requested to submit a signed commitment that three consecutive production batches will be prospectively validated and a validation report will be made available as soon as possible for evaluation by assessors or verification by the TMDA inspection team.

8. Besides the submitted GMP certificate, you should provide evidence of inspection by the ICH founding and standing members, regulatory authorities participating in the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/s), or WHO if this is available.

9. If an excipient is used as a preservative, it should be monitored during routine release and shelf life. In view of this, you are required to,

- ✓ Revise the FPP release and shelf-life specifications, including the FPP analytical procedure to include assay for the preservative and analytical methods. Your response should include

submission of the revised, signed, dated, and version-controlled FPP release and shelf-life specifications, including revised analytical procedures.

- ✓ Provide validation data for the assay method to assay the preservatives.
- ✓ Provide a revised post-approval stability study protocol and a commitment letter that you will include at least one batch annually into stability studies and monitor for all stability-indicating parameters, including assay of preservatives.

10. Required to provide overlaid IR spectra containing the primary and working standards.

11. Submit copies of dated, signed, and version-controlled specifications of the container closure system, including an appropriate identification test for the primary component of the container closure system.

12. If long-term stability data batches cover only 24 months, you are requested to submit any updated long-term stability data for the same batches to support the proposed shelf life of 36 months.

13. Compendial methods should be demonstrated to be suitable for the intended use; in this case, you must conduct analytical method verification for related substances.

14. Regarding the stability of the FPP,

- ✓ Submit revised stability protocol which includes stability-indicating parameters proposed for inclusion in shelf-life specifications
- ✓ Submit the following results one-time study for at least three batches of retained samples which is close to the expiry
- ✓ Provide a signed and dated commitment that one commercial batch will be subjected to accelerated stability studies based on the revised protocol
- ✓ Provide a signed and dated commitment for ongoing stability studies which are found to be out of specification; the report will be made available for the regulatory authority for review (22)

CONCLUSION:

After the marketing application approval, the applicant may produce and market the generic drug product, allowing the public access to a low-cost, stable, and safe drug product. The current study aims to determine the likely questions that may come up when we submit our marketing application to the agency. The questions from Module 3 (CMC Section) are the primary emphasis of this essay. The thorough analysis and compilation aid the regulatory affairs professional in minimizing errors and potential questions. It also provides a strong grasp of the crucial elements of marketing applications and the CMC portion of the dossier filing.

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PT substantially contributed to the design of the work, led the draft and revision of the critical contents of the manuscript, and agreed to be accountable for all aspects of the work. MVR substantially contributed to the draft of the manuscript, including contents & tables. ND & SV performed the operation. NJ reviewed the manuscript and revised it for content.

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The authors reported no conflicts of interest.

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