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REGISTRATION REQUIREMENTS OF GENERIC DRUGS USED IN THE TREATMENT OF LIFE STYLE DISEASES IN ASEAN COUNTRIES

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ABSTRACT

The pharmaceutical manufacturer needs to incorporate the technical requirements and all other documents of new pharmaceuticals to market their products in other countries. In this presentation it is individually discussed about the rules and regulations which are followed for drug approval process in U.S.A and Canada Any product should reach the criteria of the individual country guidelines. This study mainly discusses "Dossier preparation of generic solid orals in U.S and Canada". By following the guidance and regulations of USFDA, Health Canada, ICH and WHO filing process of pharmaceuticals in US and Canada countries will become very easy and accurate. Compilation in eCTD module will be helpful in reviewing of dossier in a very short time. In this competitive world of pharma generics, an attempt is made to highlight the difference between the two major countries registration requirements through CTD format.

KEY WORDS: Life Style Disease, Regulatory requirements, Generic drugs.

INTRODUCTION

Regulatory Affairs is the very important department in Pharmaceutical Company. For the protection of public health, government of various countries have developed the regulation for pharmaceutical, cosmetic product, pesticides, veterinary medicines, medical device, agrochemical and complementary medicines by controlling the safety and efficacy of product. Regulatory affairs department prepare the registration document which submits to the regulatory agency of various countries for approval of new drug which contain the all-important information about new drug [1]. It is called the drug master file of Common technical document (CTD). Regulatory authorities of different countries prepare their separate rules and regulations. Main aim of regulatory affairs department is to provide safe and effective medicine to people of different companies. Separate rules and regulation in different countries which must be followed by all pharmaceutical company in all over the world.

DOSSIER

Dossier is a file document submitted for the approval of drug product. It is submitted in form of CTD. CTD is a harmonized format (template) for presenting data in the ICH regions. Generic drug product is comparable to an innovator drug product in following ways.

1. In dosage form
2. Strength
3. Route of administration
4. Quality
5. Use etc

The word dossier has its English meaning as a collection of files or documents on the same subject; especially a file contains detailed information about a person or a topic. Any preparation for human use that is intended to modify or explore physiological systems or pathological states for the benefit of recipient are called as pharmaceutical product for human use [2].

The goals of the dossiers are to provide enough information to permit Regulatory Agencies' reviewers to establish the following:

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- Is the drug safe and effective in its proposed use(s) when used as directed, and do the benefits of the drug outweigh the risks?
- Is the drug's proposed labeling (package insert) appropriate, and what it contain?
- Are the methods used in manufacturing (Good Manufacturing Practice, GMP) the drug and the controls used to maintain the drug's quality adequate to preserve the drug's identity, strength, quality, and purity?

Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. The single regulatory approach for marketing authorization application (MAA) of a new drug product applicable to various countries (on the basis of single dossier) is utmost difficult. Therefore, the knowledge of exact and detailed regulatory requirements for MAA of each country should be known to establish a suitable regulatory strategy.

USFDA

The Food and Drug Administration is a Federal agency of the United states Department of Health and Human Services. The FDA is responsible for protecting and promoting public health through the regulation and supervision of Pharmaceutical drugs and many other products. The FDA regulates almost every facet of prescription drugs, including testing, manufacturing, labeling, advertising, marketing, efficiency and safety [3].
To enter into the US market, the product will need to get the approval from the US Food and Drug Administration (FDA). The applicant files a market application with FDA. After reviewing the application, FDA will decide whether to grant the product approval. Selling the product without the approval would make you a felony under the US Federal Food, Drug and Cosmetic Act.

HEALTH CANADA

Health Canada's Therapeutic Products Directorate (TPD) is the Canadian federal authority that regulates pharmaceutical drugs and medical devices for human use.

Prior to being given market authorization, a manufacturer must present substantive scientific evidence of a product's safety, efficacy and quality as required by the Food and Drugs Act and Regulations [4].

In Canada, a 'new drug' has been defined in section C.08.001 of the Food & Drug Regulations as a drug which contains a substance which has not been sold in Canada for a sufficient time and in sufficient quantity to establish its safety and efficacy. Thus, 'new drug' includes both novel products as well as drugs that are not novel but are 'new' in the sense that the particular version of the drug has not been previously marketed (as in case of a competing or a generic version of a drug that has the same properties). Under Canada's **Food & Drugs Act**, the Therapeutic Products Program (TPP) of the Federal Department of Health (Health Canada) is responsible to ensure that "new drug" meet health and safety requirements.

Both generic as well as patented products are treated as 'new drugs' by the Food and Drug Regulations because generic is equivalent, and not identical, to the patented product it replicates. The major difference between submission for a patented and a generic product is the data required to establish the safety of new drug and its clinical efficacy. For a generic drug comparative studies to establish pharmaceutical and bioequivalence with another, usually innovator's product, i.e., "Canadian Reference Product" identified in section C.08.001.1 of the Regulations is required while extensive pre-clinical, toxicity studies in animals, clinical studies and pharmacokinetic studies to establish safety and efficacy of new drug is must. The generic drug must be demonstrated to deliver the same amount of active ingredient at the same rate as the original.

Canada's Patented Medicines (Notice of Compliance) Regulations and Related Legislation

Generic challenges to brand patents in Canada are complicated by the interplay of three legislative and regulatory schemes which operate independently of one another. The first two, the Patent Act and the Food and Drug Act, reward and protect innovative drug development. Upon satisfying the conditions for patentability under the Patent Act, brand manufacturers have the right to exclude others from making, using, or selling its patented product for a period of twenty years. The purpose of this limited monopoly is to allow the innovator to charge monopoly prices for a limited period so that it may recoup costs associated with the development of innovative drugs [5]. A pharmaceutical patent is granted in exchange for advancing medicine by disclosing new and useful medicines and methods of treatment that benefit society by improving quality of life and, in some cases, longevity. The brand patentee has a cause of action for any infringement of its statutory exclusivity privileges and enjoys a presumption of validity for all of its patents.

Regulatory Guidelines for Dossier Submission in USA and CANADA

Dossier is submitted in CTD format.

CTD is an ICH standard that was adopted in a consensus process by US, Canada, Europe, Japan and other member regions. CTD is a set of specifications for application dossier for the registration of medicines and designed to be used across Europe, Japan and the United states [6]. It is an internationally agreed format for the preparation of application regarding new drugs intended to be submitted to regional regulatory authorities in participating countries. It was developed by the European Medicines Agency (EMA, Europe), the Food and Drug Administration (FDA, US) and the Ministry of Health, Labor and Welfare (Japan). The CTD is maintained by the

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [7]. Detailed subheadings for each Module are specified for all jurisdictions. The contents of Module 1 and certain subheadings of other Modules will differ, based on national requirements.

After the United States, European Union and Japan, the CTD has been adopted by several other countries including Canada and Switzerland [8]. The Paper CTD is destined to be replaced by its electronic counterpart, the eCTD. The common Technical Document is divided into five modules [9].

METERIALS AND METHODOLOGY

Dossier Preparation in US

MODULE 1 – Administrative Information

1. Forms and Cover Letter 118

Section 1.1 of ANDA contains the several forms.

1.1.2 Contains the completed, signed Application Form FDA 356h (§ 314.94(a) (1)). Applicants should provide complete contact information, including phone and fax numbers, for the agent stationed at each facility listed in the 356h form, along with detailed descriptions of the type of testing performed at each, where applicable. Applicants will be notified of failure to complete facility and testing information. Failure to provide the requested information in a timely fashion will result in the application being refused for receipt (Ref. 1). Applicants may use continuation pages, as necessary.

1.1.2 Also contains copy of the GDUFA user fee cover sheet (FDA Form 3794).

Cover letter shall include the following:

- Pre assigned ANDA number
- Established name of drug product with strength
- Brief description about present submission
- Name, Title, Signature of the responsible person and address of the applicant.

1.2.1 Contains the completed, signed Form FDA 3674, Certification of Compliance Under 42 135 U.S.C. 282(j)(5)(B) with Requirements of ClinicalTrials.gov Data Bank (42 U.S.C. 282(j)).

2. **Administrative Information**

1.3.1. Contains a U.S. Agent letter of appointment, if applicable. The U.S. agent letter of appointment is a separate document submitted in addition to the U.S. agent's signature on Form 356h, if applicable. If the applicant does not reside or have a place of business in the United States, an agent that resides or maintains a place of business in the United States must countersign the application (§ 314.50(a)(5)).

1.3.1.2 Contains a U.S. agent letter of appointment, if applicable. The U.S. agent letter of appointment is a separate document submitted in addition to the U.S. agent's signature on Form 356h, if applicable. If the applicant does not reside or have a place of business in the States, agent that resides or maintains a place of business in the United States must countersign the application (§ 314.50(a) (5)).

Contains the field copy certification (§ 314.94(d) (5)). The applicant will certify that the field copy submitted to the appropriate district office is a true copy of the technical section contained in the archival and review copies of the ANDA.

Contains the debarment certification required under the Generic Drug Enforcement Act of 1992 (section 306(k) and 306(a) and (b) of the FD&C Act (21U.S.C. 335a (k) and 335(a) and (b). The applicant must certify that it did not and will not use the services of any debarred persons in connection with the application. The applicant must also list all convictions described in the FD&C Act (section306 (k) and 306(a) and (b)). The applicant may use the following language from section 306(k) (1) for the certification required for section 1.3.3

Contains patent information and certification. Applicants are required to list each patent issued by the U.S. Patent and Trademark Office that claims the drug substance, drug product, or 170 that claims a use of the RLD that is cited by the ANDA (§ 314.94(a)(12)). FDA recommends that when providing patent information, applicants include the expiration date for each patent, whether the RLD is protected by any pediatric exclusivity, and when that pediatric exclusivity will expire. For each patent listed, the applicant must certify to one of the following paragraphs (§ 314.94(a) (12) (i) (A) (1) through (4)):

- That the patent information has not been submitted to FDA (Paragraph I certification)
- That the patent information has expired (Paragraph II certification)
- The date on which the patent will expire (Paragraph III certification)
- That the patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the ANDA is submitted (Paragraph IV certification)

If the RLD is covered by a patent claiming a method of using the listed drug and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent, the applicant must also submit a statement explaining that the method of use patent does not claim any of the proposed indications (§ 314.94(a) (12) (iii)).

Applicants submitting a Paragraph IV certification will provide the following language from § 314.94(a) (12) (i) (A) (4). Applicants submitting a Paragraph IV certification must also certify that they will provide notice to the owner of the patent(s) and the holder of the approved application that lists the patent(s) that is/are being challenged (§ 314.94(a)(12)(i)(A)(4)). The process for notice is provided in section 505(j) (2) (B) of the FD&C Act and § 314.95. Applicants should also submit an exclusivity

statement regarding their marketing intentions. This statement is relevant when the generic applicant intends to remove or Carve out any protected indication(s) from the labeling in order to gain market entry prior to a use's expiry.

3. References

1.4.2 Contains the statement of right of reference for each and every DMF referenced in the application. Applicants should submit the letter of authorization (LOA) provided to the applicant by the DMF holder which gives authorization to rely on the information in the DMF (§ 209 314.420(d)).

4. Other Correspondence

1.12.4 Contains a statement that a request for a proprietary name has been made, if applicable. An ANDA applicant requesting a proprietary name should submit that request when the ANDA is submitted to ensure an acceptable name is available at the time of approval. When requesting a proprietary name, a separate electronic submission should be made and identified as a "REQUEST FOR PROPRIETARY NAME REVIEW".

1.12.11 Must contain the basis for submission, which is the reference to the RLD (§ 314.94(a) (3)). Applicants should review the guidance for industry Variations in Drug Products that May Be Included in a Single ANDA to determine whether one or more ANDAs should be submitted for variations of a specific drug product dosage form. The applicant should provide: (1) the name of the RLD; (2) the NDA or ANDA number of the RLD; and (3) the holder of the application for the RLD.

For an ANDA based on an approved petition under § 10.30 (21 CFR 10.30) or § 314.93, this section must contain the FDA docket number and a copy of FDA's correspondence approving the suitability petition (§ 314.94(a) (3) (iii)). If the generic drug differs from the RLD in strength, route of administration, dosage form, or single active ingredient in a combination drug product, applicants must first submit a suitability petition to FDA's Division of Dockets Management to obtain permission to file their ANDA (§ 314.93; § 10.20 (21 CFR 10.20), § 10.30). The applicant must submit the suitability petition in accordance with the requirements of §§ 10.20 and 10.30 (§ 314.93(c)). The suitability petition must be approved before the ANDA is Submitted (§ 314.93(b)). The information to be included in the suitability petition is listed at § 314.93(d). FDA will review the suitability petition to determine whether the requested change from the listed drug will have an impact on the safety and effectiveness of the generic product and if any applicable requirements of the Pediatric Research Equity Act (PREA) may be waived (Ref. 7). After a suitability petition is approved for a change to a drug product, any applicant may refer to that petition as the basis of submission for an ANDA. Once an application based on a suitability petition is approved, the suitability petition may no longer be relied upon as a basis of submission. The approved drug product will become the RLD for the basis When an applicant wants FDA to designate a second RLD, the request is made through a citizen petition submitted to FDA's Division of Dockets Management in accordance with §§ 10.20 and 10.30. An applicant may submit the application only after the citizen petition has been granted.

If an applicant refers to a listed drug that has been voluntarily withdrawn from sale in the United 248 States, the applicant must submit a citizen petition under § 10.25(a) (21 CFR 10.25(a)) and 249 § 10.30 to FDA's Division of Dockets Management requesting FDA to determine whether the listed drug was withdrawn for reasons of safety or effectiveness (§ 314.122) (often referred to as a relisting petition). A relisting petition may be submitted concurrently with the ANDA. However, approval of the ANDA will be dependent on FDA's response to the petition.

Contains information demonstrating that the generic product is the same as the RLD (section 505(j) (2) (A) of the FD&C Act and § 314.94). Same means that the generic product has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as the RLD (§ 314.92(a) (1)). To demonstrate the comparison to the RLD, applicants provide:

(1) a statement that the conditions of use for the generic product have been Previously approved for the RLD (§ 314.94(a)(4));
(2) information to show that the active ingredient(s) is the same as the RLD (§ 314.94(a)(5));
(3) information to show that the route of administration, dosage form and strength Are the same as those of the RLD (§ 314.94(a) (6)); and
(4) As applicable, information to indicate the strength of the generic drug product used in the in vivo bioequivalence studies (fasting and fed) to demonstrate bioequivalence of the generic drug product to the RLD.

Applicants must also identify and characterize the inactive ingredients and demonstrate that the inactive ingredients do not affect the safety or efficacy of the proposed drug product (§ 314.94(a) (9) (ii)). This means that any differences in the identity or amount of an inactive ingredient between the proposed product and the RLD product must be identified and demonstrated as having no effect on safety or efficacy. Given that the nature of the data and information necessary to demonstrate safety and efficacy can vary by product, applicants should submit a controlled correspondence to GenericDrugs@fda.hhs.gov, consult the FDA Bioequivalence Recommendations for Specific Products Web site for current product-specific data recommendations and the Bio pharmaceutics guidance Web site, or contact the appropriate CBER review division prior to submission of the application.

FDA recommends that an applicant submit within the original application all strengths that the applicant intends to market. However, note that applicants are not

able to submit new pharmacy bulk strength in an amendment.

Contains the environmental assessment (EA) (21 CFR 25.20), environmental impact statement (EIS) (21 CFR 25.22), or claim of categorical exclusion under 21 CFR 25.30 or 21 CFR 25.31 and the justification for the exclusion. Failure to provide the EA or statement for categorical exclusion is sufficient grounds to refuse to receive the application (§ 314.101(d)(4)).

Contains a request to waive the requirement to submit evidence measuring in vivo bioavailability (BA) or demonstrating in vivo bioequivalence (BE) of the generic product (known as a bio waiver), if applicable (21 CFR 320.22). The data necessary to support a waiver request vary by product. For this reason, applicants should submit a controlled correspondence to GenericDrugs@fda.hhs.gov, consult the FDA Bioequivalence Recommendations for Specific Products Web site for current product- specific data recommendations and the Biopharmaceutics guidance's Web site, or contact the appropriate CBER review division prior to submission of the application.

5. Labeling

Contains labeling for the generic product submitted in text-based Portable Document Format (PDF),16 Microsoft Word, and Structured Product Labeling (SPL) formats (§ 314.94(a)(8)(ii). If the application is for a pharmacy bulk package product, applicants should complete and submit the Pharmacy Bulk Package Sterility Assurance Table to address sterility assurance of the drug product associated with the labeling and microbiological study data that may be submitted in the application.

Contains the draft label and labeling for each strength and container including package size. Applicants should ensure that label and labeling design do not contribute to medication error (Ref. 9). Confirm if the container closure is child resistant (CRC).

Contains side-by-side labeling comparison of container(s) and carton(s) with the 312 RLD for each strength and package size. All differences should be highlighted and 313 annotated. Applicants should indicate the RLD version used for the side-by- side 314 comparison.

Contains the prescribing and patient information in text-based PDF, Microsoft WORD and SPL formats. Applicants should identify the RLD version used for the side by side comparison.

Applicants are encouraged to review and use the Labeling Question-Based Review (QbR) model when developing labels and labeling.18 Responses to the QbR should be provided in section 1.14.1.5, as applicable. 1.14.3 Contains the RLD labeling and a comparison of that labeling to the draft labeling for the generic product. Applicants must submit side-by-side labeling comparison(s) with all differences highlighted and annotated (§ 314.94(a)(8)(iv)).

Applicants should also submit the RLD package insert, Medication Guide, one container label, and one outer carton, if applicable, for each strength and package size listed in the application (§ 314.94(a)(8)(i)). Applicants are reminded to use the most recent RLD labeling available at the Drugs@FDA Web site. 1.14.3.1 Contains side-by-side labeling (professional insert, patient insert and Medication Guide) comparison. All differences are highlighted and annotated. In addition, applicants should state that a sufficient number of patient inserts will be included in each package size. Applicants should confirm that Medication Guides will be distributed in accordance with 21 CFR 208.24. 1.14.3.3 Contains the RLD professional and patient inserts, Medication Guide, one (1) RLD container label, and one (1) RLD outer carton label for each strength and package size, if applicable.Contains the risk management plan (section 505-1 of the FD&C Act (21 U.S.C. 355-1) for products that require tools to minimize risks while preserving benefits.

Contains the risk evaluation and mitigation strategy (REMS) and all supporting documents, if the RLD has a REMS (Ref. 10). A REMS for an ANDA must have the same Medication Guide and patient package insert as does the RLD (section 505- 1(i)(1)(A) of the FD&C Act). In addition, if applicable, a REMS for an ANDA must use a single, shared system of elements to assure safe use, unless FDA waives the requirement under 505-1(i)(1)(B). However, an ANDA REMS does not include a timetable for submission of assessments of the REMS and does not include a communication plan.

Module 2 – CTD Summaries

Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use. In general, the introduction should not exceed one page. Module 2 is divided into 7 sections.

1. CTD Table of Contents
2. CTD Introduction
3. Quality Overall Summary
4. Nonclinical Overview
5. Clinical Overview
6. Nonclinical Written and Tabulated Summaries
7. Clinical Summary

2.2 Introduction to the Quality Overall Summary

Proprietary name, non-proprietary name of the drug substance, company name, dosage forms, strengths, route of administration, and proposed indications are provided.

2.3. S Drug Substance

S.1 General Information

Information from 3.2.S.1 section of Module 3 is provided.

Presentation of this section in QbR

• What are the nomenclature, molecular structure, molecular formula, and molecular weight?

• What are the physicochemical properties including physical description, pKa, polymorphism, aqueous solubility (as function of pH) hygroscopicity, melting points, and partition coefficient?

2.3. S.2 Manufacture

Information on the manufacturer, a brief description of the manufacturing process and the controls, flow diagram, a description of the source and starting material and raw materials of biological origin used in the manufacture of the drug substance are provided. A discussion of the selection and justification of critical manufacturing steps, Process controls and acceptance criteria, Highlight critical process intermediates, a description of process validation and/or evaluation, a brief summary of major manufacturing changes made throughout development and conclusions from the Assessment used to evaluate product consistency.

Presentation of this section in QbR

• Who manufactures the drug substance?

• How do the manufacturing processes and controls ensure consistent Production of the drug substance?

S.3 Characterization

A summary of the interpretation of evidence of structure and isomerism is provided.

Presentation of this section in QbR

• How was the drug substance structure elucidated and characterized?

• How were potential impurities identified and characterized?

2.3. S.4 Control of Drug Substance

A brief summary of the justification of the specifications, the analytical procedures, and validation is provided. Specification and tabulated summary of the batch analyses is imported directly from module3

Presentation of this section in QbR

• What is the drug substance specification? Does it include all the critical drug substance attributes that affect the manufacturing and quality of the drug product?

• For each test in the specification, is the analytical method(s) suitable

For its intended use, and, if necessary, validated?

• For each test in the specification, is the analytical method(s) suitable

For its intended use, and, if necessary, validated?

• For each test in the specification, what is the justification for the acceptance criterion?

S.5 Reference Standards or Materials

Description of reference standards used for the batch analysis is provided.

Presentation of this section in QbR

• How were the primary reference standards certified?

S.6 Container Closure System

A brief description of container closure system is provided

Presentation of this section in QbR

• What container closure system is used for packaging and storage of the Drug substance?

2.3. S.7 Stability

A summary of the stability conditions, batches, analytical procedures and a brief discussion of the results and conclusions, the proposed storage conditions, and the retest date or shelf life are provided. The post approval stability protocol and a tabulated summary of the stability results are directly imported from module.

Presentation of this section in QbR

• What drug substance stability studies support the retest or expiration date and storage conditions for the drug substance?

2.3. P DRUG PRODUCT

P.1 Description and Composition of the Drug Product

Description of the dosage form and composition of drug product is provided.

Presentation of this section in QbR:

• What are the components and composition of the final product?

• What is the function of each excipients?

• Do any excipients exceed the IIG limits for this route of administration?

• Do the differences between this formulation and the RLD present Potential concerns with respect to therapeutic equivalency?

P.2 Pharmaceutical Development

A brief discussion on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are provided.

Presentation of this section in QbR

• Which properties or physical chemical characteristics of the drug substance affect drug product development, manufacture, or performance?

• What evidence supports compatibility between the excipients and drug substance?

• What attributes should the drug product possess?
• How was the drug product designed to have these attributes?
• Were alternative formulations or mechanisms investigated?
• How were excipients and their grades selected?
• How was the formulation optimized?

P.3 Manufacture

Information on the manufacturer, a brief description of the manufacturing process and the controls, a flow diagram and brief description of the process validation and/or evaluation, as described in Module 3 is provided

Presentation of this section in QbR

• Who manufactures the drug product?
• Does the batch formula accurately reflect the drug product composition? If not, what are the differences and the justifications?
• What is the difference in size between the commercial scale and exhibit batches?
• Does the equipment use the same design and operating principles?
• What are the unit operations in the drug product manufacturing process?
• What is the reconciliation of the Exhibit batch? (General Process Flow chart)
• What are the in-process tests and controls that ensure each step is successful?

P.4 Control of Excipients

A brief summary of the quality of excipients, as described in Module 3, is included.

Presentation of this section in QbR

• What are the specifications for the inactive ingredients and are they suitable for their intended function?

2.3. P.5 Control of Drug Product

A brief summary of the justification of the specifications, a summary of the analytical procedures and validation (Assay and Chromatographic purity Stress conditions, Impurities found summarized, Validation Summary) and characterization of impurities is provided. Specifications and a tabulated summary of the batch analyses is provided which is directly imported from module 3

Presentation of this section in QbR

• What is the drug product specification? Does it include all the critical drug product attributes?
• For each test in the specification, is the analytical method(s) suitable for its intended use and, if necessary, validated?
• What is the justification for the drug product acceptance criteria?

P.6 Reference Standards or Materials

Description of reference standards used for the batch analysis is provided.

Presentation of this section in QbR

• How were the primary reference standards certified?

2.3. P.7 Container Closure System

A brief description and discussion of the information on container closure system is provided

Presentation of this section in QbR

• What container closures are proposed for the packaging and storage of the drug product?
• Has the container closure system been qualified as safe for use with this dosage form?

2.3. P.8 Stability

A summary of the conditions, batches, analytical procedures and a brief discussion of the results and conclusions of the stability studies and analysis of data is provided. Conclusions regarding storage conditions and shelf life and, if applicable, in-use storage conditions and shelf life should be given. A tabulated summary of the stability results and the post approval stability protocol is directly imported from M3.

Presentation of this section in QbR

• What are the specifications for stability studies, including justification of acceptance criteria that differ from the drug product release specification?
• What drug product stability studies support the proposed shelf life and storage conditions? (stability protocol)
• What is the post-approval stability protocol

Module 3 – QUALITY

Module 3 contains all of the CMC information necessary to support the application (§ 314.94(a) (9)(i)), including the information supporting and verifying what was summarized in Module 2.3. The specific placement of product quality microbiology information in Module 3 is listed in CDER's Manual of Policies and Procedures (MAPP) 5040.1 Product Quality Microbiology Information in the Common. Technical Document 30 Any analytical procedure submitted in the summaries of Module 2 should be described in sufficient detail to allow an analyst to reproduce the conditions and obtain results comparable to what is stated in the application (Ref. 15). FDA recommends that applicants submit a table of contents for Module 3.

It is recommended that applicants review the following guidance's for industry to assist in the preparation of Module 3: ANDAs: Impurities in Drug Products,

ANDAs: Impurities in Drug Substances, and ANDAs: Stability Testing of Drug Substances and Products.
As per the ICH, this module is divided into 3 sections and each section is subdivided to provide the Quality details of the drug products. The sections of this module are:

3.2. S Drug Substance
3.2. P Drug Product
3.2. R Regional Information
1. DRUG SUBSTANCE

Section 3.2.S contains the CMC information specific to the drug substance(s) (§ 314.50(d) (1) (i)). For a drug product containing more than one drug substance, the information requested for part "S" should be provided in its entirety for each drug substance. To assist in preparing data for the drug substance section, applicants should review the guidance for industry Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances.

General information

Contains general information about the drug substance including: (1) the nomenclature, (2) the structure, and (3) general properties. Section 3.2.S.1 should not include any references to the DMF.

S.1.1 Nomenclature

Information on the nomenclature of the drug substance has to be provided. For example:
• Recommended International Non-proprietary Name (INN)
• Compendia name, if relevant
• Chemical name(s)
• Company or laboratory code

3.2. S.1.2 Structure

The structural formula, the molecular formula, and the molecular mass should be provided.

3.2. S.1.3 General Properties

A list should be provided of physicochemical and other relevant properties of the drug substance. Physical and chemical properties of the drug substance such as the physical description, solubility in common solvents (e.g., water, alcohols, chloroform, acetone, etc.), quantitative aqueous pH solubility profile, polymorphism, particle size distribution, pH and pKa values, UV absorption maxima and molar absorptive, melting point, refractive index , hygroscopicity, partition coefficient, etc., are few examples.

Manufacture
S.2.1 Manufacturer(s)

Contains information related to each drug substance manufacturer including:
(1) the name and full address of the facility(ies);
(2) contact information for an agent at the facility (phone, fax numbers and email address);
(3) function or responsibility;
(4) the Type II DMF number for the API; and
(5) the Central File Number (CFN), Facility Establishment Identifier (FEI) or Data Universal Numbering System (DUNS) numbers, if known.

The applicant should also provide current good manufacturing practice (cGMP) and/or Debarment Certification of the facility that matches the information provided in FDA Form 356h. Subsections 3.2.S.2.2 through 3.2.S.2.6 may refer to the DMF. If there is no DMF referenced in the application, detailed information should be provided in these subsections.

Description of Manufacturing Process and Process Controls, Control of Materials, 3.2.S.2.4 Controls of Critical Steps and Intermediates and 3.2.S.2.6 Manufacturing Process Development: These are proprietary information for the drug substance manufacturer and hence may not be available with the applicant unless and until the applicant is the manufacturer of both the drug substance manufacturer and the drug product.

A reference to the DMF/CEP number is provided in dossiers for US, for sections 3.2.S.2.3, 3.2.S.2.4 and 3.2.S.2.6. For section 3.2.S.2.2, the reference to DMF is provided in US submissions provided. The following information is provided in Open part of the DMF.

3.2. S.2.5 Process Validation and/or Evaluation

Presentation of this section in Dossier for USA: A reference to the DMF number is provided in dossier for referring this section

3.2. S.3 Characterisation
3.2. S.3.1 Elucidation of Structure and other Characteristics

Contains characterization information for the API. FDA recommends that applicants complete the Summary Tables for the Listing and Characterization of Impurities and Justification of Limits in Drug Substance.

3.2. S.3.2 Impurities

Information on impurities should be provided. The potential and actual impurities arising from the synthesis, manufacture, degradation and metabolite are discussed. Residual solvents: The solvents used in the manufacturing of the drug substance will be eliminated to an extent possible; the drug substance manufacture should establish a limit for any solvent that is likely to occur in the final API and this limit will be established as per the ICH guideline "Impurities: Guideline for Residual Solvents Q3C". The limits of these solvents are discussed in this section.

3.2. S.4 Control of the Drug Substance
3.2. S.4.1 Specifications

Contains all information about the control of the drug substance. Contains the drug substance specifications.

These specifications include the tests, acceptance criteria, and references to methods in tabular form. If the application contains a sterile substance for use in a sterile drug product, this section will also contain the microbiological specification for the drug substance.

3.2. S.4.2 Analytical Procedures

Contains the description of analytical procedures (compendia and/or in-house). If the application contains a sterile substance for use in a sterile drug product, this section will also contain the microbiological analytical procedures used to test the drug substance.

Batch Analyses

Contains the batch analysis including the Certificates of Analysis (COAs) from both the drug substance manufacturer (s) and drug product manufacturer for the batches used to produce the exhibit batch (es) of the drug product.

Justification of Specifications

Contains the justify cation of the specifications including, but not limited to, references to compendia (e.g., USP, European Pharmacopeia (EP), and the Japanese Pharmacopeia (JP)), ICH, and/or RLD analysis. FDA recommends that applicants complete the Summary Tables for the Listing and Characterization of Impurities and Justification of Limits in Drug Substance.

3.2. S.7 STABILITY

3.2. S.7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized. Contains stability data including the retest date or expiration date of the API. Information provided should include the retest date or expiration date of the API at both the drug product manufacturing site and the drug substance manufacturing.

3.2. S.7.2 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided.

3.2. S.7.3 Stability Data

Contains stability data including the retest date or expiration date of the API. Information provided should include the retest date or expiration date of the API at both the drug product manufacturing site and the drug substance manufacturing site.

2. DRUG PRODUCT

Section 3.2.P contains detailed information known about the drug product (§ 314.50(d) (1) (ii)). During the development of the application, applicants should review the guidance's for industry Q8(R2) Pharmaceutical Development (Ref. 26) and Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (Ref. 13) and the product-specific CMC guidance's for industry (e.g., metered dose inhalers, nasal spray) as applicable. A drug product supplied with a reconstitution diluent should include a separate Module 3.2.P with the diluent information.

P.1 Description and Composition of the Drug Product

For drug products containing inactive ingredient changes permitted in accordance with § 314.94(a)(9)(iii)-(v), applicants must also identify and characterize the differences and provide information that demonstrates the change(s) does/do not affect the safety or efficacy of the drug product. This means that any differences in the identity or amount of an inactive ingredient between the proposed product and the RLD product must be identified and demonstrated as having no effect on safety or efficacy. Given that the nature of the data and information necessary to demonstrate safety and efficacy can vary by product, applicants should submit a controlled correspondence to GenericDrugs@fda.hhs.gov or consult the FDA Bioequivalence Recommendations for Specific Products Web site for current product-specific data recommendations prior to submission of the application.

3.2. P.2 Pharmaceutical Development

Contains information on the pharmaceutical development of the drug product including the pharmaceutical development report and the microbial attributes — the container closure integrity testing report for sterile product, antimicrobial effectiveness testing for multi-dose sterile products, and if the sterile drug product is packaged, as single-use/dose/multi-dose and/or pharmacy bulk. If the applicant has moved toward a Quality by Design (QbD) approach, applicants may demonstrate their methods in section 3.2.P.2. Applicants are encouraged to review FDA's information on Quality by Design for ANDAs: An Example for Modified Release Dosage Forms and An Example for Immediate-Release Dosage Forms.40 For sterile products that are reconstituted (or further diluted) and stored prior to administration, the applicant should provide microbiological studies to support the worst case post constitution or post dilution storage times, diluents, and conditions stated in the product package insert labeling. The study should be a risk assessment that shows adventitious microbial contamination does not grow (generally accepted as not more than (NMT) 0.5log10 growth) under the specified storage conditions.

3.2. P.2.1 Components of the Drug Product

3.2. P.2.1.1 Drug Substance

In this section, the compatibility of the drug substance with excipients should be discussed. Additionally, the key physicochemical characteristics such as IUPAC name, structure, empirical formula, molecular weight, mode of action, characterization of drug substance, description,

bulk density and tapped density, angle of repose, Loss on drying, Particle size distribution, pKa, reconstitution time, particulate matter and storage of the drug substance that can influence the performance of the drug product are discussed. For combination products, the compatibility of drug substances with each other should also be discussed.

3.2. P.2.1.2 Excipients

The choice of excipients listed, their concentration, and their characteristics that can influence the drug product performance are discussed relative to their respective functions. Where antioxidants/antimicrobial agents are included in the formulation, the effectiveness of the proposed concentration and the proposed limits are justified and verified by appropriate studies.

3.2. P.2.2 Drug Product

3.2. P.2.2.1 Formulation Development

A brief summary describing the development of the drug product are provided, taking into consideration the proposed route of administration and usage. The differences between Reference Listed Drug and the generic formulation are discussed and justified in this section.

3.2. P.2.2.2 Overages

Any overage in the formulation(s) should be justified. Overages can be added only to compensate the loss during manufacturing and cannot be added to compensate loss During shelf-life. In addition, overfill may need to be added to ensure the complete withdrawal of the intended dose.

3.2. P.2.2.3 Physicochemical and Biological Properties

Parameters relevant to the performance of the drug product, such as pH, ionic strength, dissolution, re-dispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, should be addressed.

P.2.2.4 comparative testing of Drug product and RLD product

The following comparison between the reference drug in respective region and the generic drug product is made in this section and any difference is appropriately justified.

3.2. P.2.3 manufacturing process development

The selection and optimization of the manufacturing process, in particular its critical aspects are explained. The scientific rationale for the choice of the manufacturing, filling, and packaging processes that can influence drug product quality. Any developmental work undertaken to protect the drug product from deterioration should also be included (e.g., protection from light or moisture). Hence, this section includes Description of the Manufacturing Process, Development of Critical Unit Operation and Comparison between Manufacturing Process Used to Produce Registration Stability Batch and Final Commercial Batch.

3.2. P.2.4 Container Closure System

The suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and Light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance.

P.2.5 Microbiological Attributes

The microbiological attributes of the dosage form are discussed. Being a sterile product intended for parenteral administration, the microbiological attributes are critical in the overall quality of the product. A single primary stability batch of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

3.2. P.2.6 Compatibility

The studies of compatibility of the drug product with reconstitution diluent(s) specified in pack insert of reference drug of respective region are discussed to provide appropriate and supportive information for the labeling. Studies cover the duration of storage reported in the labeling (e.g., 24 hours under controlled room temperature and 72 hours under refrigeration).

Control of Drug Product

Contains information supporting the controls of the drug product

Specification(s)

Contains the specifications for the drug product. These specifications include the tests, acceptance criteria, and references to methods in a tabular form. For sterile products, this section will contain the release specifications for the drug product (sterility, bacterial endotoxins, etc.). In cases where a USP monograph reports an endotoxins specification for a parenteral or intrathecal drug product, the applicant should alternatively propose a bacterial endotoxins specification based on the maximum patient dosage prescribed in the package insert labeling, not the USP monograph. The acceptance criteria for the maximum endotoxins dose to a patient are established in USP <85>.

Analytical Procedures

Contains the description of analytical procedures (compendial and/or in-house). For sterile products, this

section will contain methods for product release tests (sterility, bacterial endotoxins (if applicable), etc.)

Validation of Analytical Procedures

Contains the validation of the analytical procedure including
(1) full validation reports for in-house methods and their equivalence to USP procedures if available for the drug product;
(2) verification of USP <1226> procedures, when referenced;
(3) legible spectra and chromatograms for reference standards and test samples; and(4) the Sample Statement(s) of Availability and
(4) Identification of (a) the finished dosage form and (b) the lot numbers and strength of the drug products

Batch Analyses

Contains the batch analysis including the executed COAs for all presentations and/or strengths of the finished dosage form.

Characterization of Impurities

Contains the characterization of impurities. FDA recommends controlling all potential degradation products (Ref. 16) and processing solvents if used during manufacture in the finished dosage form. FDA recommends that applicants complete the Summary Tables for the Listing and Characterization of Impurities and Justification of Limits in Drug Substance and Drug Products.

Justification of Specification(s)

Contains the justification of the specifications including but not limited to references to compendia (e.g., USP, JP), ICH, and/or RLD analysis. FDA recommends that applicants complete the Summary Tables for the Listing and Characterization of Impurities and Justification of Limits in Drug Products.

Reference Standards or Materials

Contains information about the reference standards or materials

Container Closure System

Contains information on the container closure system including
(1) a summary of the container closure system (including data for any new resin used and technical diagrams/drawings of the container closure components, a statement whether the closure for each proposed packaging configuration is child resistant or non-child resistant and a description of markings on the cap/ferrule over seals (USP General Chapters <1> Injections);
(2) components specification and test data;
(3) packaging configuration and size;
(4) container closure testing pursuant to USP <661> and <671> (testing should be Conducted; for liquid drug products contained in plastic containers, applicants
Should also provide test data for leachable and/or extractable); and
(5) The source of supply and the supplier's address.

For controlled substances, provide a description of the tamper-evident properties of the container closure system as described in 21 CFR 1302.06. For OTC products, the applicant should confirm if the container closure system meets the requirements of 21 CFR 211.132.

Stability

The purpose of stability testing is to provide evidence on how the quality of a drug product varies with time under the influence of a various environmental factors such as temperature, humidity, and light, and to establish a shelf life for the drug product.

Post-approval Stability Protocol and Stability Commitment

Contains the postapproval stability protocol and stability commitment. If the applicant and drug product manufacturer are different entities, both will provide stability commitments. For sterile products, this section contains analytical procedures and testing schedule for maintenance of microbial product quality (e.g., container closure integrity/sterility, bacterial endotoxins, and microbial limits).

Stability Data

Contains stability data including:
(1) accelerated, long-term, and intermediate stability data, if applicable;
(2) batch numbers on stability records that are the same as the test batch;
(3) the date the stability studies were initiated; and
(4) the date the stability sample(s) were removed from the stability chamber for each testing time point (Ref. 18).

Regional Information

Section 3.2.R contains regional information for the drug substance and the drug product (§ 314.50(d) (1) (ii) (b)). 3.2. R.1.S Contains the executed batch records and blank master batch records. Applicants can refer to the DMF(s) for this information. If no DMF is referenced in the application, applicants should provide the executed and blank master batch records. 3.2. R.2.S Contains the comparability protocols (Ref. 30). 3.2. R.3.S Contains the methods validation package. This information may also be placed in section 3.2.S.4.3. 3.2. R.2.P Contains comparability protocols, if applicable.

Literature References

3.3 Contains copies of any documents referred to in the application. The documents may include published

articles, official meeting minutes, or other regulatory guidance or advice provided to the applicant. FDA recommends that the documents be provided in text-based PDF.

Module 4 – Nonclinical Study Reports

ANDAs generally do not contain data that are required for Module 4.

Module 5 – Clinical Study Reports

Module 5 contains all of the clinical study report data needed to support the application and demonstrate that the generic is bioequivalent to the RLD (§ 314.94(a) (7)). To facilitate the submission of complete data, FDA develops product- specific guidance's, summary data tables (as referenced in section III.B.2 of this guidance) and multiple guidance's on biopharmaceutics. Applicants should use an eCTD Study Tagging File for each study submitted.

5.1. Complete Study Data

Contains the tabular listing of the clinical studies submitted in the module. Contains the clinical study reports and related information. Contains the complete study data for the biopharmaceutics studies (Ref. 31) and the lot numbers and strength of products used in the BE study (ies); and documents the study type. The section will also contain information of in vivo and in vitro studies including, but not limited to 5.1. Contains reports of bioanalytical and analytical methods provided in individual study reports. If a method is used in multiple studies, the method and its validation should be included once in section 5.3.1.4 and then referenced in individual study reports.

5.2. Literature References

5.4 Contains copies of any documents referred to in the application. The documents may include published articles, official meeting minutes, or other regulatory guidance or advice provided to the applicant. One copy of all important references cited in the QOS or individual technical reports provided in section 5.3 will also be submitted in this section (Ref. 31). FDA recommends that the documents be provided in text- based PDF.

Dossier Preparation in Canada

Module 1: Administrative information and prescribing information

Module 1 is to include regional administrative documents and proposed labelling for use in the region. The information to be included in Module 1 and its outline is identified in section 4.1 of the Guidance for Industry - Preparation of New Drug Submissions in the CTD Format.

- Table of Contents (Modules 1-5)
- Application Information
- Drug Submission Application Form (HC/SC 3011)
- Submission Fee Application Form
- Submission Certification Form
- Patent Information
- Good Manufacturing Practices (GMP) and Establishment Licensing (EL) Information
- Letters of Access
- International Registration Status
- Other Application Information

This section serves as a placeholder for other administration information that may be filed by the applicant in relation to the submission.

a. Canadian Reference Product Confirmation

Confirmation that the Canadian reference product was used in the comparative bioavailability study may be provided in the form of a purchase receipt(s), signed confirmation in writing that the reference was purchased in Canada, or a photocopy of the product label(s) which clearly shows the trade name, product strength, lot #, expiry date, and Drug Identification Number (DIN) of the product administered in the Bio-study. Pursuant to paragraph (c) of section C.08.001.1 of the "Food and Drug Regulations", the use of a Canadian reference product purchased outside of Canada, must be supported by a justification statement that should be provided in this section. The justification should address all of the criteria outlined in the TPD Canadian Reference Product policy and will include supporting data (e.g., comparative dissolution) which should be provided in the relevant modules of the CTD submission (i.e., Modules 2-5).

b. Waiver Requests

Generally, results from comparative bioavailability studies should be provided in support of the safety and efficacy of each proposed product and each proposed strength included in an ANDS. In the absence of such studies, a justification supporting a waiver of this requirement should be provided in this section for each product and for each strength. For example, if there are several strengths of the proposed product, and comparative bioavailability data has not been submitted for all strengths, the sponsor should provide a scientific justification for not conducting studies on every strength of dosage form. This justification may address issues such as the nature of the kinetics of the drug (e.g., linear versus non-linear), and the proportionality of the strengths for which a waiver is sought to the strength on which a comparative bioavailability study was conducted.

c. Certificates of Analyses

Certificates of Analyses should be provided in this section in order to verify the potency (as a percent of the label claim) for both the Test and Reference products.

Product Labelling: Product Monograph

The Product Monograph for second and subsequent market entry products must provide information directly relevant to the safe and effective use of the new drug. Please

note that the conditions of use for the new drug must fall within the conditions of the use of the Canadian reference product. A copy of the current labelling and Product Monograph for the reference product must be included in the submission (in this section). Any differences between the Product Monographs must be annotated to supporting data. Copies of data or references to support such differences must be included in the submission. Please note that the labelling must be current at the time the NOC is issued.

The CS-BE is pivotal in the review process. It should provide a comprehensive, integrated summary of the overall content of information in the submission as it pertains to the comparability of the product with the Canadian reference product of proven safety and effectiveness under the proposed conditions of use. This should include a scientific rationale and justification for the study design used, the parameters assessed and the standards applied. It must also be cross-referenced to the supporting documents provided in Module 5 (Clinical Study Reports). The CS-BE template provides placeholders for the following information (which may not necessarily be a component of the clinical study report(s) submitted in Module 5).

Physicochemical Characteristics

This section should provide information characterizing the physicochemical properties of the drug, e.g., pKa, molecular weight, solubility in water (g/mL), chirality and polymorphism.

Pharmacology

This section should include a concise synopsis of the salient features of the drug's pharmacologic actions, e.g., site and mechanism of action.

Pharmacokinetics

Information on the absorption, distribution, metabolism and elimination of the drug should be presented here. The nature and extent of any first pass effect, whether plasma concentrations are directly related to dose (i.e., are the pharmacokinetics linear), and values of half-life (T½), clearance, volume of distribution and fraction excreted should be established on the basis of the information summarized in this section. This information, together with that provided under Drug Product Classification, is important in establishing the type and number of studies to be conducted in support of each ANDS.

• Absorption- Information characterizing the following properties of the drug is required; area under the curve (AUC), time of maximum observed concentration (Tmax), maximum observed concentration (Cmax), time of onset of action and food effect on absorption. Other characteristics of absorption kinetics (e.g., stereo specificity and dose or concentration dependence of absorption) must also be reported.

• Distribution- Degree of protein binding, information identifying sites of distribution is required, including reference to whether the drug crosses the blood-brain barrier.

• Metabolism- Identify the site(s) and pathway(s) of metabolism. Metabolites should be characterized as to biological/pharmacological activity and whether or not drug metabolizing enzymes are induced. Specify the degree of first-pass metabolism and whether metabolism is capacity limited.

• Elimination- Identify the route(s), percent of elimination and terminal half-life (T½).

Summary of the Bioavailability/Bioequivalence Studies

This portion of the CS-BE should include summaries of each study performed to establish the bioavailability and bioequivalence of each formulation and be cross referenced to the supporting documents provided in Module 5 (Clinical Study Reports). All requests for waivers and justification statements should be included in Module 1.2.8 (Other Application Information).

Table of Contents of Module 3

A Table of Contents for the filed application should be provided.

Body of Data

Drug Substance (Name, Manufacturer)

General Information (name, manufacturer)

Nomenclature (name, manufacturer)

Information on the nomenclature of the drug substance should be provided. For example: Recommended International Non-proprietary Name (INN); Compendial name if relevant; Chemical name(s); Company or laboratory code; Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN), and Chemical Abstract Service (CAS) registry number:

Structure (Name, Manufacturer)

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

General Properties (Name, Manufacturer)

A list should be provided of physicochemical and other relevant properties of the drug substance.

Manufacture (Name, Manufacturer)

Manufacturer(s) (Name, Manufacturer)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

Description of Manufacturing Process and Process Controls

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For example: A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.

Control of Materials (Name, Manufacturer)

Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) 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 (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate.

Controls of Critical Steps and Intermediates (Name, Manufacturer)

Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Process Validation and/or Evaluation (Name, Manufacturer)

Process validation and/or evaluation studies for aseptic processing and sterilisation should be included.

Manufacturing Process Development (Name, Manufacturer)

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.

Characterization (Name, Manufacturer)

Elucidation of Structure and other Characteristics (Name, Manufacturer)

Confirmation of structure based on e.g., synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.

Impurities (Name, Manufacturer)

Information on impurities should be provided.

Specification (Name, Manufacturer)

The specification for the drug substance should be provided.

Analytical Procedures (Name, Manufacturer)

The analytical procedures used for testing the drug substance should be provided.

Validation of Analytical Procedures (Name, Manufacturer)

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.

Batch Analyses (Name, Manufacturer)

Description of batches and results of batch analyses should be provided.

Stability (Name, Manufacturer)

Stability Summary and Conclusions (Name, Manufacturer)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Stability Data (Name, Manufacturer)

Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Drug Product (Name, Dosage Form)

Description and Composition of the Drug Product (Name, Dosage Form)

A description of the drug product and its composition should be provided. The information provided should include, for example: Description of the dosage form; Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any) the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications); Description of accompanying reconstitution diluent(s); and Type of

container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

Pharmaceutical Development (Name, Dosage Form)

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 instructions 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 (critical parameters) 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.

Formulation Development (Name, Dosage Form)

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.

Overages (Name, Dosage Form)

Any overages in the formulation(s) described in 3.2.P.1 should be justified.

Physicochemical and Biological Properties (Name, Dosage Form)

Parameters relevant to the performance of the drug product, such as pH, ionic strength, dissolution, dispersion, reconstitution, particle size distribution, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.

Manufacturing Process Development (Name, Dosage Form)

The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified. And the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

Container Closure System (Name, Dosage Form)

The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product).

Microbiological Attributes (Name, Dosage Form)

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

Compatibility (Name, Dosage Form)

The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.

Manufacture (Name, Dosage Form)
Manufacturer(s) (Name, Dosage Form)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

Batch Formula (Name, Dosage Form)

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

Description of Manufacturing Process and Process Controls (Name, Dosage Form)

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogenizer) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 3.2. P.3.4. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated. Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (3.2.P.3.3).

Controls of Critical Steps and Intermediates (Name, Dosage Form)

Critical Steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled. Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Process Validation and/or Evaluation (Name, Dosage Form)

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilization process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2.A.2, if necessary.

R Regional Information

Any additional drug substance and/or drug product information specific to each region should be provided in section R of the application. Applicants should consult the appropriate regional guidelines and/or regulatory authorities for additional guidance. Where validation is still to be completed, a summary of the studies intended to be conducted should be provided.

Literature References

Key literature referenced about quality of products should be provided, if applicable.

Module 4 – Nonclinical Study Reports

ANDAs generally do not contain data that are required for Module 4.

Module 5: Clinical Study Reports

Table of Contents for Module 5

This section should include the table of contents of Module 5 only. The table of contents for Module 5 should be presented in accordance with ICH M4: Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use.

Tabular Listing of all Clinical Studies

Clinical Study Reports

5.3.1 Biopharmaceutics Studies

5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports Clinical study reports are to be structured in accordance with ICH E3: Structure and Content of Clinical Study Reports.

This section of the submission should include a detailed description of each study performed to establish the relative bioavailability and therefore, bioequivalence of each formulation. The reports should be based on raw quantitative and qualitative data. The reports will require the compilation of summary tables and graphs that should be presented as described in the TPD guidance Conduct and Analysis of Bioavailability and Bioequivalence Studies -- Part A, and Part B. The clinical study report must include factual and concise descriptions of the methods and materials used, presentation of the results and critical evaluation of the study design, analytical methodology and statistical analysis of data. It should be presented in sufficient detail to allow an independent evaluation of the drug. It is important that the bioequivalence report state, clearly and unambiguously, the chemical and pharmaceutical formulations used in the study of the drug. Detailed accounts of, and reasons for, all protocol modifications, deviations, or violations must be highlighted, explained and cross-referenced to the original study protocol. Generally, it is unlikely the clinical study report for a comparative bioavailability or bioequivalence trial will include all of the sections outlined in the ICH E3 guidance document. It is anticipated that some specific issues within various sections will not be applicable. For example, within section 11.4 (Efficacy Results and Tabulations of Individual Patient Data), it is unlikely that the following sections will be applicable.

However, section 11.4.2.2 (Handling of Dropouts or Missing Data) and 11.4.7 (Efficacy Conclusions) will be applicable and should be addressed.

Sections of the clinical study report (E3) that are not applicable should appear in the table of contents for the clinical study report with the words “not applicable”; however, it is not necessary to include tabs for these non-applicable sections in the body of the report. If the table of contents for Module 5 of the dossier identifies the sections of the clinical study report (E3), sections that are “not applicable” should be handled in the same manner as described for the table of contents for the report. The outline for a clinical study report for a comparative bioavailability study has been provided below. All sections are to be addressed unless identified as “not applicable”. For applicable sections, the ICH E3: Structure and Content of Clinical Study Reports guidance document should be followed with respect to structure and content unless otherwise specified below.

1. Title Page
2. Synopsis
3. Table of Contents for the Individual Clinical Study Report

4. List of Abbreviations and Definition of Terms
5. Ethics
6. Investigators and Study Administrative Structure

This section of the report, in addition to the information detailed in ICH E3, should include the geographic location of the study facility (ies) as well as the name, address, telephone, and fax numbers of individuals responsible for the performance of the study.

7. Introduction
8. Study Objectives
9. Investigational Plan

Overall Study Design and Plan - Description

This section should provide a concise description of the study design (in 2-3 sentences) as outlined in the ICH E3 guidance document.

Appropriateness of Measurements

Usually, blood is the biological fluid sampled to measure concentrations of the analyte in serum or plasma. However, there may be circumstances where other biological fluids may be sampled. Alternatives to blood sampling should be discussed in this section including a rationale for the biological sample collected. The total volume of fluid collected per subject per phase of the study should be discussed with respect to subject safety and the potential impact on plasma concentration data.

In light of advances in analytical methodology it is expected that allowances made in the past for basing a bioequivalence assessment on the metabolite (rather than the parent compound) may no longer be valid. Therefore, in most cases, the bioequivalence assessment should be based on the parent compound.

Data Quality Assurance

Statistical Methods Planned in the Protocol and Determination of Sample Size

Statistical and Analytical Plans

This section should be addressed as outlined in the ICH E3 guidance. In general terms, this section provides a description of the analyses planned in the protocol. This section emphasizes the analyses, comparisons and statistical tests that were planned whereas section 11.4.2 emphasizes the statistical analyses that were actually used.

Determination of Sample Size

With reference to section 3.3 of the TPD guidance document, Conduct and Analysis of Bioavailability and Bioequivalence Studies - Part A: Oral Dosage Formulations Used for Systemic Effects, a discussion of sample size, including a subject sample size calculation should be provided. The actual number of subjects enrolled, and the number completing the study should be provided under section 10.1 (in accordance with ICH E3). 9.8 Changes in the Conduct of the Study or Planned Analyses

10. Study Patients
    Disposition of Patient
    Protocol Deviations
11. Efficacy Evaluation

Data Sets Analysed

Generally, this section (as described in ICH E3) is not applicable to comparative bioavailability studies.

Demographic and Other Baseline Characteristics

With reference to the TPD guidance on the Conduct and Analysis of Bioavailability and Bioequivalence Studies --Part A, and Part B, where appropriate the following information should be summarized.

Efficacy Results and Tabulations of Individual Patient Data

Analysis of Efficacy

Statistical/Analytical Issues

This section should be addressed as outlined in the ICH E3 guidance. For a description of the data that should be recorded, the pharmacokinetic parameters, the statistical analyses to be performed, and the format that should be used to present the results, refer to TPD guidance Conduct and Analysis of Bioavailability and Bioequivalence Studies -- Part A, and Part B, and the Expert Advisory Committee on Bioavailability -- Report C.

Briefly, the measured individual and mean analyte concentrations for each formulation should be tabulated. Any differences from the submitted study protocol must be identified and explained. These data should also be provided in the computer readable form. Mean and individual linear as well as semi-log concentration-time

Profiles for each formulation should be provided the regression lines, based upon at least four points during the terminal log-linear phase of the curve, used to estimate the terminal disposition rate constant should also be displayed. The pharmacokinetic parameters should be tabulated for each subject by formulation. Their method of estimation should also be provided.

The submitted analyses of variance (ANOVA) should include the appropriate statistical tests of all effects in the model. The ANOVA should include all data from all subjects. Exclusion of data points or subjects must be justified. An ANOVA should be carried out on the raw (non-transformed) data and Tmax on the logarithmically (natural) transformed AUCT, AUCI and Cmax data. Results should be summarized in tabular form, including the information specified in the aforementioned guidance. Results for AUCT and Cmax ratios for test Vs reference product, and the confidence interval about the mean AUC (and about the mean Cmax, when required), must be expressed as both uncorrected and corrected for measured content (potency). If alternate statistical approaches are

used, a discussion should be provided including a justification statement.

Each subject withdrawal and the reason for the withdrawal should be provided. The timing of the decision to withdraw the subject should be identified (e.g., before sample analysis). If the protocol for handling dropouts or withdrawals was not followed, a rationale for violating the protocol should be provided.

Analytical Validation Report

"Measurement Methodology "in section 5.3.1.4 (Reports of Bioanalytical and Analytical Methods for Human Studies).

In vitro-In vivo Correlation Study Reports

In vitro dissolution studies that provide BA/BE information, including studies used in seeking to correlate in vitro data with in vivo comparisons, should be placed in this section. Reports of in vitro dissolution tests used for batch quality control and/or batch release should be placed in the Quality section of the CTD formatted submission.

Please note that at the present time the TPD does not accept in vitro-in vivo correlation studies as evidence of safety and efficacy in lieu of pivotal in vivo studies. This Module is included in the outline only as a placeholder for future use should such correlation studies be developed and considered acceptable.

Reports of Bioanalytical and Analytical Methods for Human Studies

Bioanalytical or analytical methods for BA/BE or in vitro dissolution studies should ordinarily be provided in the individual clinical study reports. However, where a method is used in multiple studies, the method and its validation should only be included once in section 5.3.1.4 and referenced in the appropriate individual clinical study reports.

Measurement Methodology

Evidence that the analytical method used is suitable, reliable and reproducible must be submitted. Without being limited to the following, the submitted information should include:

i. Standard operating procedures (SOPs) for those aspects of analysis that are critical to the assessment of the validity of the methodology used, such as sample preparation and stability, criteria for the acceptance/rejection of data (e.g., repeat analysis, QC's, standards curves, etc.), etc.

ii. A description of the methodology,

iii. Copies of literature references cited, and details of the specific attributes of the method as used by the analytical facility as described below.

i, ii In general, it is not necessary to provide information of a proprietary nature. Should such information be required it can be submitted, in confidence, directly to the TPD.

In order to determine that the analytical method has yielded reliable and reproducible results, it must be characterized and validated. Validation comprises both pre-study and during study performance. For a previously validated analytical method not used on a regular basis, the continued validity of the method should be confirmed before sample analysis. Having confirmed the continued validity of the method, for routine analysis, the study parameters identified should be provided. Furthermore, if analysis

RESULTS & DISCUSSIONS

Compilation of dossier for generic drugs (ANDS) in Canada and U.S includes all modules as per ICH guidelines in CTD format electronically. Majority of bulk drugs companies (sponsors) file their dossiers by collecting the all relevant data from R&D, their documents from QC dept. and which are finally authorized by QA dept. regarding particular product.

Comparative BA/BE studies information of that generic drug are gathered from Contract Research Organizations(CRO's) which will conduct clinical trials, bioavailability studies of different drugs especially. All these data included in the Dossier should be submitted to the Agent of our company who is very familiar with pre-submission meetings and updating guidelines of that regulatory authority. The Agent verify the Dossier and inform to the company if any requirements, documents, letters are needed and collect them and finally submit to the federal regulatory authority i.e., Health Canada (TPD) or USFDA. Experts and scientists will review of these submissions as per regulatory norms regarding Quality, Safety & Efficacy of that product compared to Canadian reference product or U.S reference product. Once the dossier is found to be acceptable, then sponsor will get the NOC/DIN for that particular generic drug. Then the generic product is acceptable to market that product in Canada or U.S.

CONCLUSION

The regulatory requirements for this ANDS submission, guidelines and regulations of Health Canada, USFDA and proceeding ANDS by considering CTD format with ICH guidelines which were discussed in the Methodology of this submission. In this dissertation mainly focused on the Modules and brief introduction regarding the CTD Format and ICH guidelines also. Compilation of documents for Dossier preparation of pharmaceuticals in Canada and U.S are also briefly mentioned in the Methodology. Here by included that the abbreviated new drug dossier preparation, development and also review of submission in Canada and U.S. Here by concluded that the brief information regarding Dossier preparation of generic drugs in Canada and U.S also explored in this.

REFERENCES

1. FDA Forms listed above are available at http://www.fda.gov/aboutFDA/ReportManuals Forms/Forms/default.htm.
2. Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use (ICH M4).
3. The Common Technical Document for the Registration of Pharmaceuticals for human Use: Safety (ICH M4S).
4. ICH guideline: M4Q Guideline, ICH Official website, http://www.ich.org/fileadmin/Public_Web_Site/ ICH_ Products/ CTD/M4_R1_Quality/M4Q R1_.pdf.
5. Suzanne Marie Porter Canada's Patented Medicines (Notice of Compliance) Regulations: Removing Inefficiencies to Encourage Generic Competition University of Toronto, © Copyright Suzanne Marie Porter 2011. https://tspace.library. utoronto.ca/bit stream/1807/31388/1/Porter_Suzanne_M_201111_LLM_thesis.pdf.
6. Health Canada, guidance for industry: Management of Drug Submissions, Published by authority of the Minister of Health, Revised Date: 2013/12/19; Effective Date:2013/12/19.Health Canada website. Available at:http://www.hc- sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/ mgmt- gest/mands_gespd-eng. pdf. Accessed: June 23, 2014.
7. Health Canada, Draft guidance for industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format. Published by authority of the Minister of Health. Draft Date 2004/05/12.Health Canada website.http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prod pharma/ draft_ebauche_ctdbe-eng.pdf.
8. Health Canada, Quality overall summary - chemical entities (New Drug Submissions/ Abbreviated New Drug Submissions) (QOS-CE (NDS/ANDS)), Health Canada website,http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb- dgpsa/pdf/prodpharma /qoscendsands sgqecpdnpadn-eng.pdf, Accessed September 14, 2014.
9. Information on DMF is from http://www.fda.gov/Drugs/DevelopmentApprovalProcess/.