

Review Article

Comparison of Regulatory Requirements for Generic Drugs Dossier Submission in United States, Europe and Canada

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ABSTRACT

Common Technical Document (CTD) provides a standardized structure for regulatory submissions that is acceptable in all ICH countries. Although the CTD makes multinational filings easier, there are significant differences in the dossier submission requirements in these countries. This study put forth the differences in registration requirements for generics in United States. Generic drugs in US they are approved under the Abbreviated New Drug Application. Bioavailability and Bioequivalence study data is critical in the generic drug approval process. For marketing authorization of the generic medicinal product in Europe, the applicant should submit abridged application to the relevant authority. The ability to accommodate country specific requirements and understand regulatory differences will have a substantial impact on the success of its multi country submissions strategy. Generic manufacturers must file an Abbreviated New Drug Submission (ANDS), and the manufacturer is obligated to establish bioequivalence of their drug to the 'Canadian Reference Product' (CRP). Medicinal products are highly regulated in the European Union (EU) and are subject to a separate, complicated system of approval procedures.

Keywords: CTD, Generic drug, CRP, Bioequivalence, ANDS.

INTRODUCTION

A **generic drug** (generic drugs, short: generics) is a drug defined as "a drug product that is comparable to a brand/reference listed drug product in dosage form, strength, quality and performance characteristics, and intended use. It has also been defined as a term referring to any drug marketed under its chemical name without advertising or to the chemical makeup of a drug rather than to the advertised brand name under which the drug is sold. Although they may not be associated with a particular company, generic drugs are subject to the regulations of the governments of countries where they are dispensed. Generic drugs are labeled with the name of the manufacturer and the adopted name (nonproprietary name) of the drug¹. A generic drug must contain the same active ingredients as the original formulation. According to the U.S. Food and Drug Administration (FDA), generic drugs are identical or within an acceptable bioequivalent range to the brand-name counterpart with respect to pharmacokinetic and pharmacodynamic properties. In most cases, generic products are available once the patent protections afforded to the original developer have expired. In most countries of the world, patents give 20 years of protection. However, many countries/regions, e.g. the European Union and the USA may grant up to 5 years of additional protection for drugs ("patent term restoration").

A generic drug is identical--or bioequivalent--to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price¹.

Dossier for generic drug filling shall be submitted in the form of CTD in Europe, US & Canada. Generic Drugs are approved under **ANDA** (Abbreviated New Drug Application) in **USA** and **MAA** (Marketing Authorization Application) in **Europe** & **ANDS** (Abbreviated New Drug Submission) in **Canada**. All drug products sold in Canada must be approved by the Therapeutic Products Directorate.

The Canadian pharmaceutical market is the eighth largest in the world, accounting for about two percent of the world market by sales. Canada also has the fourth fastest growing pharmaceutical industry after

China, the US and Spain and has shown a steady growth trend. It is the responsibility of the Therapeutic Products Directorate (TPD) of the Health Products and Food Branch (HPFB), Health Canada, to ensure that all drugs used by the public are safe and effective for specific conditions and of high quality.²

European Medicines Agency is a decentralised body of the European Union (EU), located in London. Its main responsibility is the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. The Agency is responsible for the scientific evaluation of applications for European marketing authorisations for both human and veterinary medicines (centralised procedure). Under the centralised procedure, companies submit a single marketing-authorisation application to the Agency. Once granted by the European Commission, a centralised (or 'Community') marketing authorisation is valid in all EU and European Economic Area-European Free Trade Association (EEA-EFTA) states (Iceland, Liechtenstein and Norway).

The use of the Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines of the Council of Europe (EDQM) in support of changes to the drug substance is not accepted for Biologics (Schedule D drugs) but is under review in pharmaceuticals for use in humans (Human Pharmaceuticals). On the other hand, for Biologics (Schedule D drugs), the use of Transmissible Spongiform Encephalopathy (TSE)- CEP may be provided to support raw materials, auxiliary materials and reagents at risk of transmitting BSE/TSE agents. Sponsors are encouraged to contact the appropriate Directorate for further guidance³.

OVERVIEW OF ICH

The ICH was founded in April 1990 at a meeting of the European Federation of Pharmaceutical Industries Association (EFPIA) in Brussels. ICH is a unique undertaking that brings together the drug regulatory authorities and the pharmaceutical industry of Europe, Japan and the United States.

The ICH Steering Committee (SC) is the governing body that oversees the harmonization activities. The ICH operates via the ICH Steering Committee. The ICH Steering Committee consists of the six parties and an IFPMA representative. The IFPMA hosts the ICH Secretariat and participates as a non-voting member of the SC and the six parties represent the regulatory authorities and the pharmaceutical industry of the European Union, Japan and USA⁴.

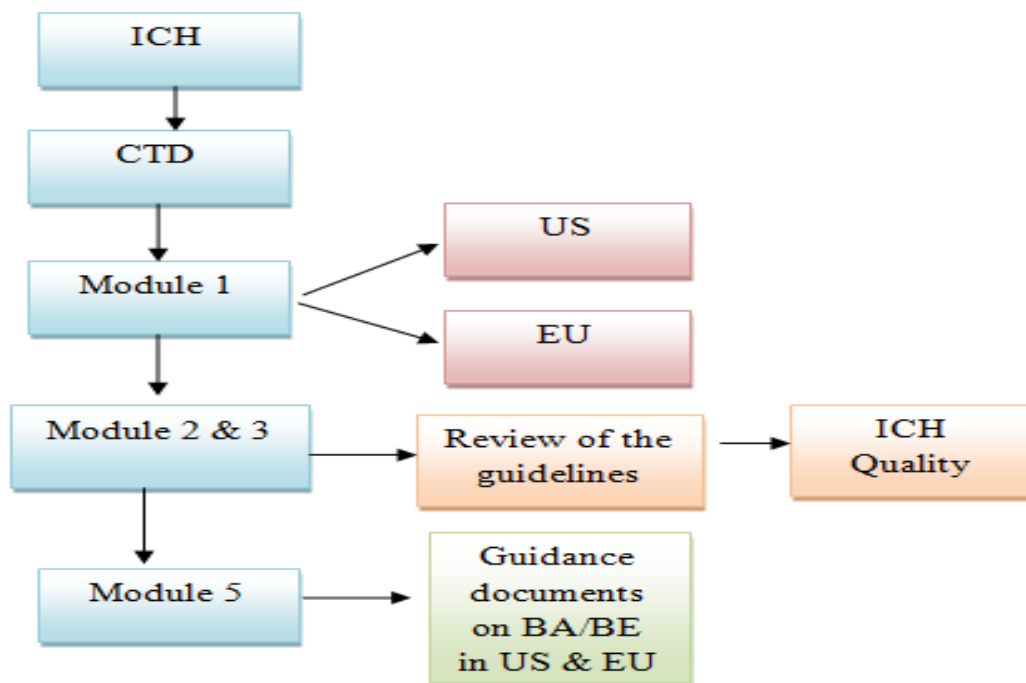


Fig. 1: Overview of ICH⁴

The observers are WHO, EFTA and Health Canada. They act as a link between the ICH and non-ICH countries.

ICH Objectives

- To prevent duplication of clinical trials in humans;
- To minimize the use of animal testing without compromising safety and effectiveness;
- To streamline the regulatory assessment process for new drug applications; and
- To reduce the development time and resources for drug development.

Preparing and Organizing the CTD⁴

In CTD, the display of information should be unambiguous and transparent, so as to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (EU) and 8.5 x 11 paper (US). A margin of at least 0.75 inches from the bound edge of the printed page is required to prevent information from being obscured and to place the paper in a binder. Narrative text is submitted in Times New Roman 12 point font. Generally, font sizes 9 to 10 points are considered acceptable in tables. Ten point fonts are recommended for footnotes. Acronyms and abbreviations should be defined the first time they are used in each module. The CTD is divided into five modules:

- Module 1 - *Administrative and prescribing information*
- Module 2 - *Overview and summary of modules 3 to 5*
- Module 3 - *Quality (Pharmaceutical documentation)*
- Module 4 - *Non clinical document safety (toxicology studies)*
- Module 5 - *Clinical document efficacy (Clinical studies)*

Introduction of CTD⁵

CTD is common technical documents which is a major project of the ICH to avoid the duplication and translation into regional language work of a single application. Through this, an applicant can file one single application to more than one country at a time for the registration of their drug product. According to ICH, all the technical requirements for the application of drug approval were harmonized in CTD format which are scientifically more elaborate by USFDA in Quality Overall Summary (QOS) and Overall efficacy (includes clinical overview and clinical summary). This way of presentation of the registration documents has increased the efficiency in the FDA review process.

The main Areas of Harmonization for CTD are

- ❖ Safety Pharmacology
- ❖ Clinical pathology
- ❖ Immunotoxicology
- ❖ Juvenile toxicity studies
- ❖ Statistical methods in certain studies like mutagenicity, carcinogenicity and toxicokinetic studies during
- ❖ The 1st phase of ICH. So far, this has not been discussed in any ICH EWG and could be considered as a future topic.
- ❖ Recommendations for additional/ alternative methods of testing carcinogenicity.

The Common Technical Document is organized into five modules⁸. The contents of Module 1 are different according to the competent authorities of the United States (FDA), the European Agency for the Evaluation of Medicinal Products (EU). The modules are present in the triangular format which all the modules are the part of CTD except module 1 which is not the part of CTD and is different for different country. The different modules are as follows:

Module 1: It is related to submit the regional and administrative information to the national regulatory agencies in which an applicant desires to file a market approval application as per their regulatory guidelines. Prescribing informations (such as labeling and package inserts) also come under this module. It is totally different for different country.

Module 2: It consists of the overviews and overall summaries related to the chemistry, manufacture, control (CMC), non-clinical, and clinical studies results conducted to prove the quality, safety and efficacy of the drug product. This module includes the summaries of module 3, 4, and 5.

Module 3: Quality - It covers the complete pharmaceutical and technical aspects which can affect the quality of the drug product. From the formulation and development department (pharmaceutical development report) to the manufacturing (GMP), analysis and testing (GLP), packaging, storage conditions, stability studies of the drug product.

Module 4: Non-clinical study reports – it covers the complete pharmacological, toxicological study reports and informations equivalent to the quality of the drug to provide the evidence of the safety of the drug product.

Module 5: Clinical study Reports – The clinical trials and their reports carried out on the human beings to list the desired effect of the drug product are included in this section. It is to provide to the regulatory authority containing the informations which prove the efficacy of the drug. For generic drugs, the applicant only has to prove the bioavailability similar to that of innovator or branded drug only. To conduct such bioequivalence studies (BA-BE), healthy volunteers are selected and to be conducted in a controlled manner.

Before CTD/eCTD application for the submission of a drug application, the procedure was different as per the country wise. In US, NDA, ANDA, BLA, Integrated summary of Safety (ISS), integrated summary of Efficacy (ISE) was submitted for the approval of the product as shown in the figure, so many duplicate copies were required to make according to the FDA.

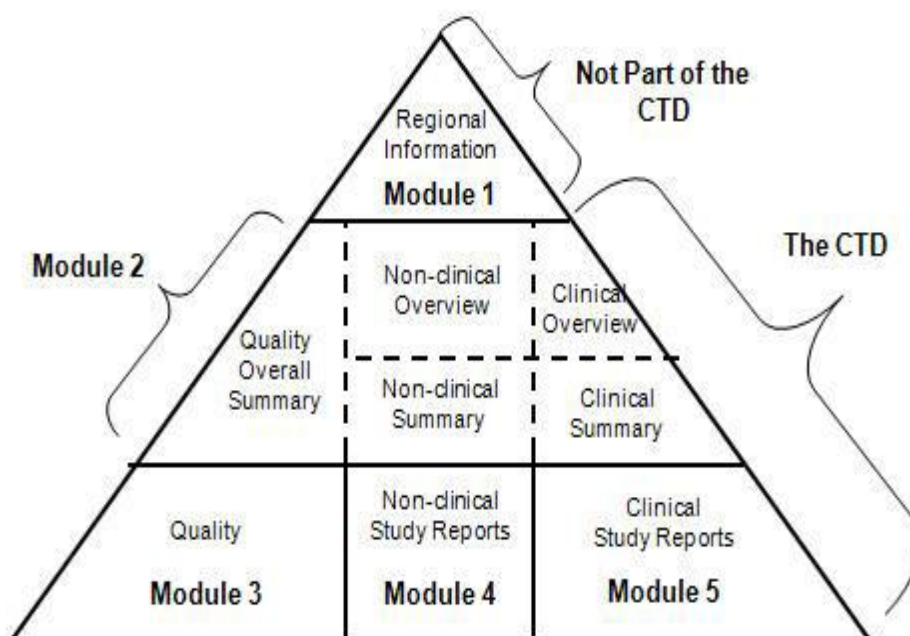


Fig. 2: CTD Triangle⁵

OBJECTIVE

The main objective is to have comparison regulatory requirements for generic drug dossier submission in different countries by following guidelines and regulations of different countries and procedures by considering CTD along with ICH regulations.

- Procedure of the generic dossier and their requirements in selected countries.
- Comparison of the generic dossier procedures of selected countries.
- To get knowledge of documents required for that ANDS filing and the process of review.
- To understand the regulatory guidelines in drug approval procedures.

- To understand the importance of regulatory guidelines.

METHODOLOGY

- It was done mainly on collection of the regulatory requirements for approval of generics. The research is carried out with the data collected by analyzing terms of following aspects.

Types of study

- The study was conducted with an objective to chalk out the regulatory framework for generic drug filing, legislations and guidelines. The major emphasis has been provided to regulatory requirements of EUROPE, CANADA and UNITED STATES. In addition emphasis is made on the administrative documents in the emerging nations.

Source of data

- Major part of the proposed data was collected by means of following sources:

Literature review

- Typically reviewed the dossiers, covered the books and regulatory guidelines published officially by government authorities, including the academic journals, online journals, market research reports, news paper articles and world fact and other resources.

Internet using the web page content

- The literature was collected using so many search engines. Online books, journals also served as a good source of information. Key words in the search involved CTD, ICH, generic drug registration requirements, how the drugs are approved, guidance for industry, check lists, exclusivities, food and drug act, administrative.

Archival study

- Complete and thorough study of regulatory information produced by Regulatory authority of Canada in it's website. <http://www.hc-sc.gc.ca/>. Regarding the exact definitions of new drugs and their limitations, considered the Food and Drug Act and Regulations.
- To better understand the Legal frame work of Canada, assault the meetings of the higher officials who are in contact with the regulatory authorizes and observed the previous recordings related to discussions deals with the requirements for health Canada.
- Health Canada is pleased to announce the finalisation of the *Guidance Document: Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format*. It defines the regional requirements of regulatory activities in CTD format, found in Modules 1 and 3.
- Release of the Health Canada *Draft Guidance Document: Quality (Chemistry and Manufacturing): New Drug Submissions (NDSs) and Abbreviated New Drug Submissions (ANDSs)* *Quality (Chemistry and Manufacturing) Guidance Document: NDSs and ANDSs* (draft, 2001); *Stability Testing of Existing Drug Substances and Products* (2003); *Impurities in Existing Drug Substances and Products* (draft, 2005).

DISCUSSION

GENERIC DRUG DOSSIER SUBMISSION IN US

Generic Drugs are approved under **ANDA** (Abbreviated New Drug Application) in **USA**. New drugs, like other new products, are developed under patent protection. When patents or other periods of exclusivity expire, manufacturers can apply to the FDA to sell generic versions.

In order to file ANDA all required items should be in proper order (organization). Detail information is available under Regulation 21 CFR 314.50, 21 CFR 314.94 and 21 CFR 314.440

Office of Generic Drug (OGD) strongly encourages submission of the bioequivalence, chemistry and labeling portions of an application in electronic format¹⁰.

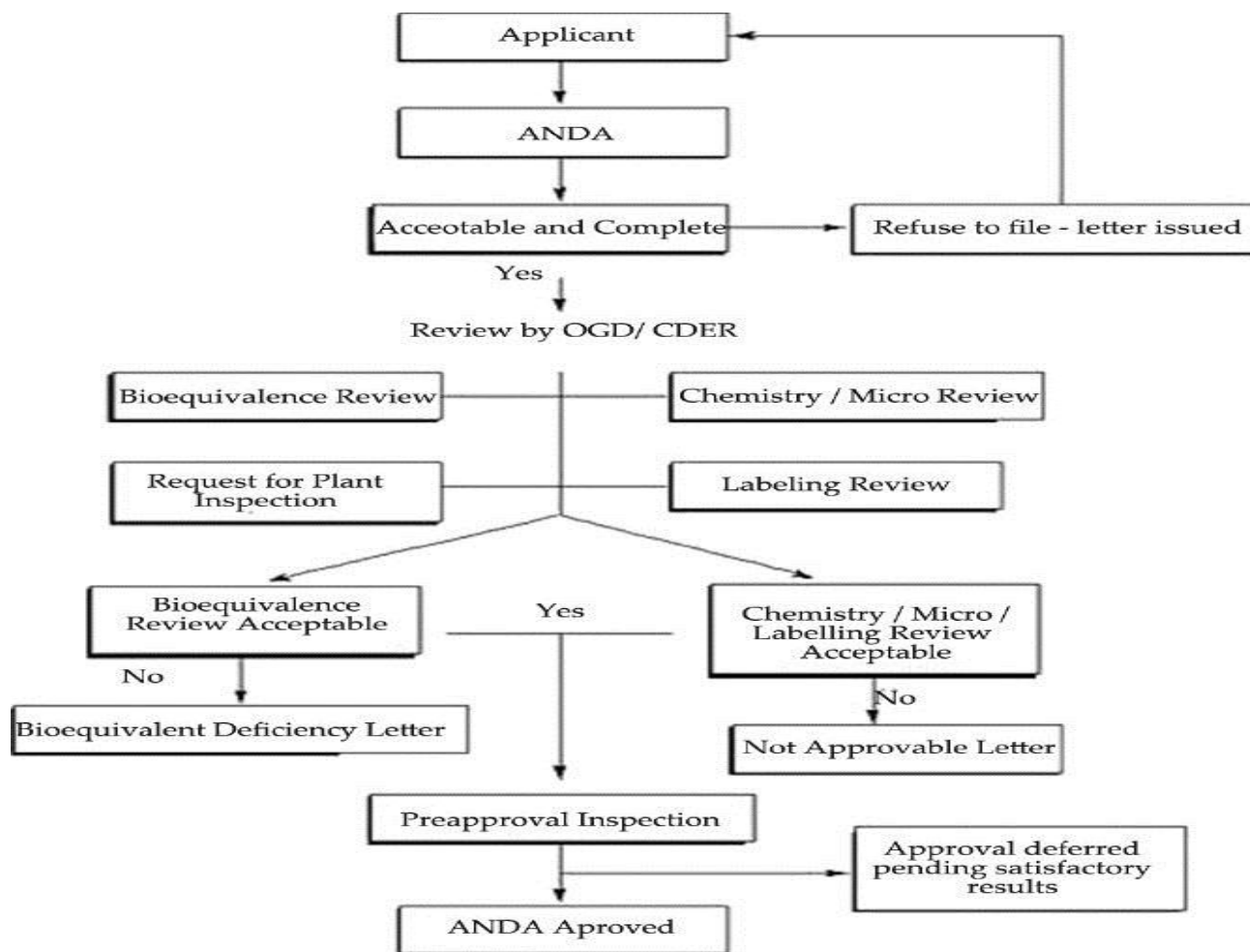


Fig. 3: Generic drug approval process¹⁰

An abbreviated new drug application contains data, which when submitted to FDA's 'Center for Drug evaluation and research' (CDER), office of generic drugs, provides for review and ultimate approval of a generic product. Once approved, the applicant may manufacture and market generic drug product to provide a safe, effective, low cost alternative to American public.

This guidance identifies the information an applicant should include to ensure that a complete, high-quality application is submitted to FDA. FDA has previously published guidance on the filing process, including the refuse-to-receive standards, which should be reviewed thoroughly to avoid common deficiencies found in ANDA submissions.

FDA has issued several guidance documents specific to the CTD and eCTD submissions. The information contained in these guidances focuses on the technical aspects of filing a CTD application and should be reviewed thoroughly prior to submitting an ANDA. This guidance addresses the content of the CTD for an original ANDA.

The CTD is comprised of the following modules:

- Module 1: Administrative information;
- Module 2: CTD Summaries;
- Module 3: Quality;
- Module 4: Nonclinical study reports; and
- Module 5: Clinical study reports.

The sections that follow in this guidance detail the information to be submitted in the applicable Modules, sections, and subsections.

Module 1 – Administrative Information¹¹**1. Forms and Cover Letter**

Section 1.1 of the ANDA submission contains several forms.

1.1.2 Contains the completed, signed Application Form FDA 356h.

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

1.2 Cover letter.

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

2. Administrative Information

1.3.1.2 U.S. agent letter of appointment, if applicable.

1.3.2 Field copy certification.

1.3.3 Contains the debarment certification required under the Generic Drug Enforcement Act 1992 of the FD&C Act. The applicant must certify that it did not and will not use the services of any debarred persons in connection with the application.

1.3.4 Financial certification

1.3.5 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 that claims a use of the RLD that is cited by the ANDA. 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:

- 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)

Applicants submitting a Paragraph IV certification

I, (name of applicant), certify that Patent No. _____ (is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product) for which this application is submitted.

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.

4. Other Correspondence

1.12.4 Contains a statement that a request for a proprietary name has been made, if applicable. 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. 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.

1.12.12 Contains information demonstrating that the generic product is the *same* as the RLD. *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.

1.12.14 Contains the environmental assessment (EA) (21 CFR 25.20), environmental impact statement (EIS) (21 CFR 25.22). Failure to provide the EA or statement for categorical exclusion is sufficient grounds to refuse to receive the application.

1.12.15 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 biowaiver), if applicable (21 CFR 320.22).

5. Labeling

1.14.1 Contains labeling for the generic product submitted in text-based Portable Document Format (PDF), Microsoft Word, and Structured Product Labeling (SPL) formats.

1.14.1.1 The draft label and labeling for each strength and container including package size.

1.14.1.2 Side-by-side labeling comparison of container(s) and carton(s) with the RLD for each strength and package size.

- 1.14.1.3 Prescribing and patient information in text-based PDF, Microsoft WORD and SPL formats.
- 1.14.1.4 Pharmacy Bulk Package Sterility Assurance Table, if applicable.
- 1.14.1.5 Labeling history.
- 1.14.3 RLD labeling and a comparison of that labeling to the draft labeling for the generic product.
- 1.14.3.1 Side-by-side labeling (professional insert, patient insert and Medication Guide) comparison.
- 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.
- 1.16.1 Contains the risk management plan for products that require tools to minimize risks while preserving benefits.
- 1.16.2 Contains the risk evaluation and mitigation strategy (REMS) and all supporting documents, if the RLD has a REMS. A REMS for an ANDA must have the same Medication Guide and patient package insert as does the RLD.

B. Module 2 – CTD Summaries¹²

1. *Quality Overall Summary*

2.3 Contains the Quality Overall Summary (QOS), which provides an overview of the chemistry, manufacturing, and controls (CMC) section of the application. The QOS summarizes what is known about the

Drug substance (the active pharmaceutical ingredient (API)) in section **2.3.S**

Drug product in section **2.3.P**

All information provided in the summary needs to be accurate and supported by information, data, or justification included in Module 3 or other parts of the application.

Applicants should use the Question-Based Review (QbR) model when writing their summaries. The QbR model assists applicants in developing their QOS by providing specific questions that, when answered, ensure adequate information is submitted for FDA review. The QOS

- should not exceed 40 pages of text, excluding tables and figures.
- Introduction should not exceed one page.
- should not exceed 80 pages for biotech and products manufactured using more complex process.

2.3.S Drug substance

2.3. S.2 Manufacture

2.3. S.3 Characterization

2.3. S.4 Control of Drug Substance

2.3. S.5 Reference Standards or Materials

2.3. S.6 Container Closure System

2.3. S.7 Stability

2.3.P. Drug product

2.3. P.1 Description and Composition of the Drug Product

2.3. P.2 Pharmaceutical Development

2.3. P.2.1 Components of the Drug Product

2.3. P.2.1.1 Drug Substance

2.3. P.2.1.2 Excipients

2.3. P.2.2 Drug Product

2.3.P.2.3 Manufacturing Process Development

2.3. P.2.4 Container Closure System

2.3. P.3 Manufacture

2.3. P.4 Control of Excipients

2.3. P.5 Control of Drug Product

2.3. P.6 Reference Standards or Materials

2.3. P.7 Container Closure System

2.3. P.8 Stability

2. Clinical Summary

Contains the submission of summary data critical to the determination of bioequivalence. The tables provide a format for applicants to in vitro BE studies as well as the results of in vitro dissolution testing. These model tables are available on the FDA ANDA Forms and Submission Requirements Web site.

2.7 Contains the completed tables in Microsoft Word and text-based PDF file.

2.7 Clinical summary

2.7.1 Summary of biopharmaceutical studies and associated analytical methods

2.7.1.1 Background and overview

2.7.1.2 Summary of results of individual studies

2.7.1.3 Comparison and analyses of results across studies

2.7.4 Summary of clinical safety

C. Module 3 – Quality¹²

Module 3 contains all of the CMC information necessary to support the application, including the information supporting and verifying what was summarized in Module 2.3.

It is recommended that applicants review the following guidances for industry to assist in the preparation of Module 3: *ANDAs: Impurities in Drug Products* (Ref. 16), *ANDAs: Impurities in Drug Substances*, and *ANDAs: Stability Testing of Drug Substances and Products*.

3.2.S Drug Substance

3.2.S.1. General information

3.2.S.1.1 Nomenclature

3.2.S.1.2. Structure

3.2.S.1.3. General properties

3.2.S.2 Manufacturer

1. Name and full address of the facility(ies)

2. Contact information for an agent at the facility (phone, fax numbers and email address)

3. U.S. Agent's name(if applicable)

4. Specify function or responsibility

5. Type II DMF number for the API

6. Central File Number (CFN), Facility Establishment Identifier (FEI) or Data Universal Numbering System (DUNS) numbers, if known.

3.2.S.3 Characterisation

3.2.S.4 Control of drug substance

3.2.S.4.1. Specification

3.2.S.4.2 Analytical procedures

3.2.S.4.3 Validation of analytical procedures

3.2.S.4.4 Batch analyses

3.2.S.4.5 Justification of specification

3.2.S.5 Reference standards or materials

3.2.S.6 Container closure system

3.2.S.7 Stability

3.2.P. Drug product

3.2.P.1 Description and composition of the drug product

3.2.P.2 Pharmaceutical development

3.2.P.3 Manufacture

3.2.P.3.1 Drug product manufacturers

3.2.P.3.2 Batch formula

3.2.P.3.3 Description of manufacturing process and process controls

3.2.P.3.4 Controls of critical steps and intermediates

3.2.P.3.5 Process validation and/or evaluation

3.2.P.4 Control of excipients

3.2.P.4.1 Specifications

3.2.P.4.2 Analytical procedures

3.2.P.4.3 Validation of analytical procedures

3.2.P.4.4 Justification of specifications

- 3.2.P.5 Control of drug product
 - 3.2.P.5.1 Specifications
 - 3.2.P.5.2 Analytical procedures
 - 3.2.P.5.3 Validation of analytical procedures
 - 3.2.P.5.4 Batch analysis
 - 3.2.P.5.5 Characterisation of impurities
 - 3.2.P.5.6 Justification of specifications
- 3.2.P.7 Container closure system
- 3.2.P.8 Stability
 - 3.2.P.8.1 Stability summary and conclusion
 - 3.2.P.8.2 Post approval stability protocol and stability commitment
 - 3.2.P.8.3 Stability data
- 3.2.R.S Regional information[Drug Substance and Drug Product]
 - 3.2. R.P.1 Executed Batch Records
 - 3.2. R.2.P Comparability Protocols
 - 3.2. R.3.P Methods Validation Package

D. Module 4 – Nonclinical Study Reports

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

E. Module 5 – Clinical Study Reports¹²

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. To facilitate the submission of complete data, FDA develops product-specific guidances, summary data tables, and multiple guidances on biopharmaceutics. Applicants should use an eCTD Study Tagging File for each study submitted.

1. Complete Study Data

5.2 Contains the tabular listing of the clinical studies submitted in the module.

5.3 Contains the clinical study reports and related information.

5.3.1 Contains the complete study data for the biopharmaceutic studies 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:

Synopsis

- Study report
- Protocol and amendments
- All case report forms
- List of independent ethics committees (IECs) or institutional review boards (IRBs) and consent and/or assent forms
- IRB approval letters for protocol, amendments, and consent/assent forms
- List and description of investigators and sites
- Number of subjects enrolled in each site
- Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer
- Listing of subjects receiving test drug(s) from specified batch
- Randomizations scheme
- Audit certificates and reports
- Documentation of statistical methods and interim analysis plans
- Documentation of interlaboratory standardization methods of quality assurance procedures if used etc
 - 5.3.1.2** Contains the comparative BA and BE study reports (e.g., fasting studies, fed studies).
 - 5.3.1.3** Contains in vitro-in vivo correlation study reports (e.g., comparative dissolution data).
 - 5.3.1.4** 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.

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. FDA recommends that the documents be provided in text-based PDF.

What are the basic generic drugs requirements?

Same active ingredients
 Same route of administration
 Same dosage form
 Same strength
 Same conditions of use
 In active ingredients already approved in similar NDA

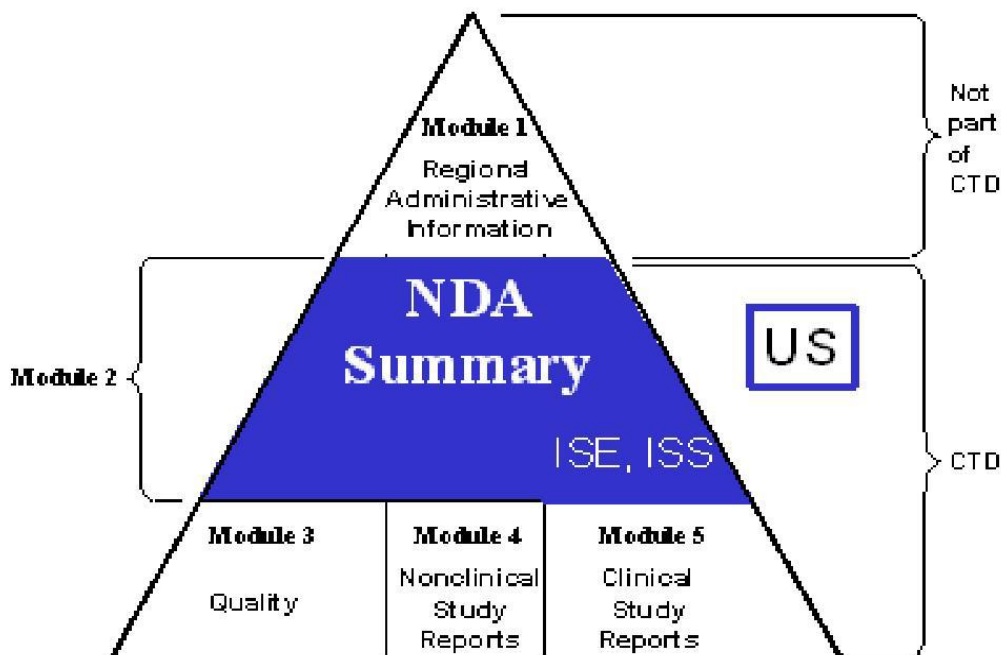


Fig. 4: USFDA Drug Registration Triangle¹⁰

GENERIC DRUGS IN CANADA

If the manufacturer can establish that their product follows the same route of administration and the same conditions for use as the CRP, while ensuring safety, efficacy and quality, the generic drug is given clearance to be marketed in Canada. For instance, British Columbia has the highest share of generic prescriptions at 50.6% while Quebec has the lowest (39.1%)^[13].

The fourth largest pharmaceutical manufacturer in Canada behind brand-name companies Johnson & Johnson (\$1.121 billion) AstraZeneca (\$1.172 billion) and Pfizer (\$2.397 billion).

Table 1: Presentation of Information in the Common Technical Document (CTD) Format¹⁴

Module Number	Title and Main Section Headings	Cross-Reference to Modules	Binder/Label colour	Number of Paper Copies
1	Administrative and Product Information			
1.0	Correspondence			
1.1	Table of Contents (Modules 1 to 5)			
1.2	Administrative Information			
1.3	Product Information			
1.4	Health Canada Summaries	2, 3, 4 and 5	Red	1*
1.5	Environmental Assessment Statement			
1.6	Regional Clinical Information			
1.7	Clinical Trial Application and Clinical Trial Application-Amendment			

1.A	Specific Requirements Appendix			
2	Common Technical Document (CTD) Summaries			
2.1	CTD Table of Contents (Modules 2 to 5)	2 to 5		
2.2	CTD Introduction	2 to 5		
2.3	Quality Overall Summary	3		
2.4	Nonclinical Overview	2 and 4	Yellow	1*
2.5	Clinical Overview	2 and 5		
2.6	Nonclinical Written and Tabulated Summaries	2 and 4		
2.7	Clinical Summary	5		
3	Quality			
3.1	Table of Contents of Module 3		Blue	1*
3.2	Body of Data			
3.3	Literature References			
4	Nonclinical Study Reports			
4.1	Table of Contents of Module 4		Green	1
4.2	Study Reports			
4.3	Literature References			
5	Clinical Study Reports			
5.1	Table of Contents of Module 5		Black	1
5.2	Tabular Listing of All Clinical Studies			
5.3	Clinical Study Reports			
5.4	Literature References			

* For combination products that require a joint review an additional copy of Modules 1, 2, and 3 is required.

Module 1: Administrative and Product Information¹⁵

Module 1 identifies placeholders, defined by the numerical items listed in the Module 1 Table of Contents (ToC), for all administrative and product information documentation.

Module 1.0 Correspondence

Module 1.0.1 Cover Letter

Any data being submitted to Health Canada should be accompanied by a cover letter.

- Requested AD HOC PSUR - submitted as a one-time request (the requestor should be specified in the cover letter);
- Voluntary PSUR - unsolicited information
- Requested Periodic PSUR - requested by Health Canada, for example (e.g.) follow-up to a Risk Management Plan (RMP) or post-authorization commitment;
- PSUR-C (confirmatory) - submitted to support the fulfilment of a Notice of Compliance with Conditions (NOC/c).

Module 1.0.2 Life Cycle Management (LCM) Table

- The Life Cycle Management (LCM) Table is a specific requirement for filing a regulatory activity in eCTD format, and should be placed in this section.

Module 1.0.3 Copy of Health Canada Issued Correspondence

- Clarifax (during screening or review);
- Notice of Deficiency (NOD);
- Notice of Non-Compliance (NON);
- Not Satisfactory Notice (NSN);
- Post-Notice of Compliance Letters (Post-NOC);

Module 1.0.4 Health Canada Solicited Information

- Solicited information is defined as information requested by Health Canada. Responses to these requests are to be provided in Question and Answer format, and placed in this section. The answers should summarize the response and cross-reference the supporting data that is to be placed in the appropriate Module of the regulatory activity. **No supporting data** is to be provided in this section.

Module 1.0.5 Meeting Information.

Module 1.0.6 Request for Reconsideration Documentation

Module 1.0.7 General Note to Reviewer

Module 1.1 Table of Contents (ToC)

Module 1.2 Administrative Information

*Module 1.2.1 Application Forms**Module 1.2.2 Fee Forms**Module 1.2.3 Certification and Attestation Forms***Module 1.2.4 Intellectual Property Information****Module 1.2.4.1 Patent Information**

All patents listed on the Patent Register for the Canadian reference product used to establish bioequivalence for the second person's submission by filing a Form V: Declaration Re: Patent List as per section 5 of the *PM (NOC) Regulations*.

Module 1.2.4.2 Data Protection Information

The term of data protection is effective from the date of the issuance of the Notice of Compliance (NOC) and extends to eight years (eight and one-half years if relevant paediatric clinical trial data is submitted).

Module 1.2.5 Compliance and Site Information**Module 1.2.5.1 Clinical Trial Site Information Forms**

Completed Clinical Trial Site Information Forms (CTSI) must be provided in this section for each proposed clinical trial site.

Module 1.2.5.2 Establishment Licensing**Module 1.2.5.3 Good Clinical Practices****Module 1.2.5.4 Good Laboratory Practices****Module 1.2.5.5 Good Manufacturing Practices****Module 1.2.5.6 Good Pharmacovigilance Practices****Module 1.2.5.7 Other Compliance and Site Information Documents****Module 1.2.6 Authorization for Sharing Information**

The regulatory activity with other regulatory authorities (or vice versa), and/or to access other (third party) drug regulatory activities, DMF and Site Reference Files (SRF) should be provided in this section.

Module 1.2.7 International Information

Information on the product application, approved indications and marketing status in other countries/regions provide useful contextual information should be provided in this section when requested.

Module 1.2.8 Post-Authorization Information

The following information should be included in this section:

- *Market Notification Forms*
- *Post-Authorization Commitments*
- *Notices of Change (Level III) forms*
 - ❖ *Post-Notice of Compliance (NOC) Changes: Notices of Change (Level III) Forms* are to be placed in this section. These forms should not be confused with the Annual Notification, which is not included in the scope of this document.
- *Notice of Decision and Summary Basis of Decision*

Module 1.2.9 Other Administrative Information**Module 1.3 Product Information****Module 1.3.1 Product Monograph**

Within the sections of the annotated Product Monograph, the text should also be cross-referenced by number to the *References or Selected Bibliography* section at the end of the Product Monograph.

Articles from publications listed in the References section should be cited in accordance with the current edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, International Committee of Medical Journals Editors (ICMJE). When reference is made to a publication not provided in Modules 2 - 5, copies of the reference material should be provided in this section.

Module 1.3.2 Inner and Outer Labels**Module 1.3.3 Non-Canadian Labelling**

If the drug product has been marketed outside Canada, the applicant is encouraged to supply the monograph or package inserts approved in other jurisdictions, clearly identifying them by country or region.

Module 1.3.4 Investigator's Brochure**Module 1.3.5 Reference Product Labelling**

Module 1.3.6 Certified Product Information Document

A copy of the non-annotated (clean) and annotated CPID are to be placed the text of the annotated copy at the time of filing should be cross-referenced to the corresponding sections of Module 3, while any further revisions should reflect all changes that have been made, including Level III changes.

Module 1.3.7 Look alike/Sound alike Assessments**Module 1.3.8 Pharmacovigilance Information**

Module 1.3.8.1 Pharmacovigilance Plan

Module 1.3.8.2 Risk Management Plan

Module 1.3.8.3 Risk Communications

Module 1.3.8.4 Other Pharmacovigilance Information

Module 1.4 Health Canada Summaries

Module 1.4.1 PSEAT-CTA

The completed Protocol Safety and Efficacy Assessment Template - Clinical Trial Application should be placed in this section.

Module 1.4.2 Comprehensive Summary: Bioequivalence

The completed Comprehensive Summary: Bioequivalence (CS -BE) for all *pivotal* comparative bioavailability (bioequivalence) studies should be placed.

Module 1.4.3 Multidisciplinary Tabular Summaries

This section is a placeholder for tables that contain information that is applicable to more than one discipline.

Module 1.5 Environmental Assessment Statement

As per the New Substances Program Advisory Note 2006-04, New Substance Notification (NSN) packages for substances used in product regulated by the Food and Drugs Act must be submitted to the New Substances Division at Environment Canada.

Module 1.6 Regional Clinical Information

Module 1.6.1 Comparative Bioavailability Information

Specific requirements for *pivotal* comparative bioavailability (bioequivalence) studies should be placed in this section. These specific requirements include, but are not limited to:

- Canadian Reference Product (CRP) Confirmation;
- Requests for waivers and justification statements;
- Verification of potency of the Test and Reference products (Certificates of Analysis);
- Bioavailability/Bioequivalence (BA/BE) data sets (required for all types of *pivotal*) comparative bioavailability (bioequivalence) studies.

Module 1.6.2 Company Core Data Sheets

Module 1.6.3 Priority Review Requests

Module 1.6.4 Notice of Compliance with Conditions

All documentation relating to an NOC/c is to be placed in this section only. These documents include, but are not limited to, the following:

- Letter of undertaking;
- Qualifying Notice;
- Dear Health Care Professional Letters (DHCPL);

Module 1.7 Clinical Trial Information

Module 1.7.1 Study Protocol

Module 1.7.2 Informed Consent Forms

Module 1.7.3 Canadian Research Ethics Board (REB) Refusals

Module 1.7.4 Information on Prior-related Applications

Module 2: Common Technical Document (CTD) Summaries¹⁵**2.3 Introduction to the Quality Overall Summary**

- What information should be provided in the introduction?

- Proprietary Name of Drug Product
- Non-Proprietary Name of Drug Product
- Non-Proprietary Name of Drug Substance
- Company Name
- Dosage Form
- Strength(s)
- Route of Administration
- Proposed Indication(s)
- Maximum Daily Dose
- **2.3.S DRUG SUBSTANCE**

2.3.S.1 General Information

Brief details about the nomenclature, molecular structure, molecular formula, and molecular weight are included. Apart from the above, details about

- Physical Description
- pKa
- Hygroscopicity
- Stereo chemistry
- Polymorphism
- Specific optical rotation
- Water content
- Solubility Characteristics
- Hygroscopicity
- Melting Point
- Partition Coefficient

2.3.S.2 Manufacture

Details about the manufacturer i.e., name, address, telephone, fax, contact person details, site of production, DMF number, DUNS number, US agent details of the company should be mentioned.

2.3.S.3 Characterization

- Details about the ICH class, limits and In-House limits of residual solvents used in the manufacturing process should be given in a tabular format.
- Information about the genotoxic impurities and threshold of toxicological concern should be provided.

2.3.S.4 Control of Drug Substance

- Drug substance specifications and analytical methods should be provided. Each analytical method used for testing the drug substance is to be suitable for its intended use, and are to be either based on pharmacopeial methods or must have been validated by the drug substance manufacturer or drug product manufacturer or by both.

Table 2: Drug Substance Specifications¹⁶

Drug Substance Specification			
Test	Acceptance Criteria	Analytical Procedure	Test Results
Description	White to almost white crystalline powder		White crystalline powder
Solubility	Practically insoluble in water. Freely soluble in ethanol and methylene chloride		Complies
Identification	(A) Infrared Absorption: The infrared absorption spectrum of the substance under examination should be similar to the USP/Phr.Eu reference spectrum of XYZ. (B) HPLC: The retention time of		(A) Complies

Drug Substance Specification			
Test	Acceptance Criteria	Analytical Procedure	Test Results
	the XYZ peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay.		(B) Complies
Specific rotation	Between – 45°C and – 49°C (t = 20°) On anhydrous basis.		-46.4°
Crystallinity	Must comply with USP/Phr.Eu		Complies
pH	Between 9.0 and 11.0, in a mixture of methanol and water (1:1) containing 2 mg per ml		10.0
Loss on drying (TGA)	Not more than 4.5 % w/w		0.98%
Ambient to 70°C 70°C to 130°C	1.8 % w/w to 2.6 % w/w		1.8%
Residue on ignition	Not more than 0.3 % w/w, the charred residue being moistened with 2 ml of Nitric acid and 5 drops of sulfuric acid.		0.1% w/w
Heavy metals	Not more than 0.0025% w/w		Less than 0.0025%
Assay by LC	94.5 % -103.0 % w/w On the anhydrous basis (Report as is for information)		99.6% w/w
Bacterial Endotoxins	Not more than 0.35 EU/mg		< 0.0768 EU/mg
Microbial Limits: Total aerobic microbial count Total Combined mould and yeast count	Not more than 100 cfu/g Not more than 10 cfu/g		30 cfu/g Less than 10 cfu/g
Related Substances and Total impurities	Not more than 2.0 %		As per ICH Q3
Residual Solvents: Ethanol Acetone Methylene chloride (dichloromethane) Acetonitrile	Between 7500 and 13000 ppm Not more than 500 ppm Not more than 100 ppm Not more than 100 ppm		
Thiocyanate content	Not more than 5 ppm		
Platinum (Pt)	Not more than 5 ppm		

- **2.3.S.5 Reference Standards**
- **2.3.S.6. Container closure system**
- **2.3.S.7 Stability**
- **2.3.P DRUG PRODUCT**
- **2.3.P.1 Description and composition**
-

Formulation Comparison between RLD and Proposed Generic Drug Product		
Reference listed drug	Proposed generic drug product	Function
Xxx	Xxx	Active Ingredient
Yyy	Yyy, USP	Buffering Agent
Zzz	Zzz, NF	pH Adjustment

- **2.3.P.2 Pharmaceutical Development**
- Brief summary of the development studies conducted to develop the dosage form, the formulation, manufacturing process, container closure system and microbiological attributes are included.
- Summary on critical parameters that have influence on batch reproducibility, performance and stability should also be discussed.

2.3.P.2.1 Components of the product

2.3.P.2.1.1 Drug substance

2.3.P.2.1.2 Excipients

2.3.P.2.2 Drug product

- The same conditions of use (indication), route of administration, dosage form, and strength as the RLD.
- The same active and inactive ingredients in the same concentration as the RLD.
- Meet the same finished product quality attributes as the RLD.
- Have a 2-year expiry period.

2.3.P.2.3 Manufacturing process development**2.3.P.2.4 Container closure system****2.3.P.3 Manufacture****2.3.P.4 Control of Excipients****2.3.P.5 Control of drug product****Table 4: Drug product release specifications¹⁵**

Drug Product Release Specifications (3.2.P.5.1)			
Tests	Acceptance Criteria	Analytical Procedure	Batch
Description	A white to off-white lyophilized powder or cake		
Identification by HPLC	The retention time of the XYZ peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard Preparation		
Ph	6.0 – 7.0		
Water content	Not more than 2.0% w/w		
Test for particulate matter	Foreign matter: Free from visible particles		
Test for sterility	Must comply		
Bacterial Endotoxins	Not more than 0.7EU/mg of XYZ		
Assay of XYZ by HPLC	90.0 % to 120.0% of label claim		
Total impurities	Not more than 3.0%		
Reconstituted Time	Not more than 3 minutes		

Validation of Analytical procedures**2.3.P.6 Reference standards and materials****2.3.P.7 Container Closure System****2.3.P.8 Stability****Module 3: Quality**

This section provides, the chemical-pharmaceutical and biological information for both chemically active substances and biological medicinal products. It should include a table of contents to direct the reviewer around the document and should be followed by the body of data in the following order

Section S- Drug substance

Section P- Drug product

Section A- Appendices which include information referenced in the core dossier and adventitious agents' safety evaluation i.e. transmissible spongiform encephalopathy agents.

Section R - Any regional information e.g. executed batch records, Method Validation, Package, Comparability Protocols (USA only) and the process validation scheme for the drug product (EU only).

Section C - contains any key literature references, if applicable.

Quality Module is divided in to two parts

3.2.S Drug Substance

3.2.P. Drug Product

3.2.S Drug Substance

3.2.S.1 General Information

3.2.S.1.1 Name and Nomenclature

Quality Module is divided in to two parts

3.2.S Drug Substance

3.2.P. Drug Product

3.2.S Drug Substance**3.2.S.1 General Information**

3.2.S.1.1 Name and Nomenclature

3.2.S.1.3 General properties

3.2.S.2. Manufacturer

3.2.S.2.1 Manufacturer(s)

3.2.S.2.2 Descriptions of manufacturing process and process controls

3.2.S.2.3 Control of materials

Table 5: Control of Materials¹⁵

Sl. No.	Name of the material	Used in Stage
Key Starting material		
1	Xyz	X
List of Raw material		
2	Xxx	Y
3	Yyy	Z
List of solvents		
4	Xxx	X
5	Yyy	Y

3.2.S.2.4 Controls of critical steps and intermediates

3.2.S.2.5 Process validation and/or Evaluation

3.2.S.2.6 Manufacturing process development

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of structure & other characteristics

3.2.S.3.2 Impurities

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specifications

3.2.S.4.2 Analytical Procedures

Substance [Manufacturer] Test Methods

3.2.S.4.3 Validation of analytical procedure

3.2.S.4.4 Batch analysis

1. Supplier's certificate of analysis**2. Applicant certificate of analysis**

3.2.S.4.5 Justification of specification

3.2.S.5 Reference standards or materials**3.2.S.6 Container closure system****3.2.S.7 Stability**

3.2.S.7.1 Stability summary and conclusion

Packaging**Stability conditions****Table 6: Stability conditions for packaging¹⁵**

Type of study	Stability conditions	Frequency of testing
Accelerated	Temperature : 25°C ± 2°C Humidity : 60% ± 5% RH	Initial, 1, 2, 3 and 6 months
Long term	Temperature : 2 – 8°C	Initial, 3, 6, 9, 12, 18, 24, 36, 48 and 60 months

CONCLUSION

3.2.S.7.2 Post approval stability protocol and stability commitment

Specifications for stability study

Table 7: Frequency of testing and conditions¹⁶

Type of study	Stability conditions	Frequency of testing
Accelerated	Temperature : 25°C ± 2°C Humidity : 60% ± 5% RH	Initial, 1, 2, 3 and 6 months
Long term	Temperature : 2 – 8°C	Initial, 3, 6, 9, 12, 18, 24, 36, 48 and 60 months

Stability commitment**3.2.P Drug Product**

This section contains complete details of the drug product.

3.2.P.1 Description and composition of the drug product**3.2.P.2 Pharmaceutical development**

3.2.P.2.1.1 Drug substance (name, dosage form)

3.2.P.2.1.2 Excipients (name, dosage form)

3.2. P.2.2 Drug product

3.2.P.2.2.1 Formulation development

3.2.P.2.2.1.2 Formulation rationale

3.2.P.2.2.1.3 Forced degradation Study

3.2.P.2.2.1.1 Evaluation of generic listed drug

In this section, the forced degradation study will be performed to evaluate the stability of the finished product, under forced degradation conditions (extremes of heat, light, acid, base and peroxide stress) in the presence of proposed excipients.

3.2. P.2.2.2 Overages

In this section overages used in the formulation should be discussed if any.

3.2. P.2.2.3 Physiochemical and biological properties

3.2. P.2.3 Manufacturing process development**3.2. P.2.4 Container closure system****3.2.P.2.5 Microbiological attributes****3.2.P.2.6 Compatibility****3.2.P.3 Manufacture****3.2.P.3.2 Batch Formula (name, dosage form)****3.2.P.3.3 Description of manufacturing process and process controls (name, dosage form)****3.2.P.3.4 Controls of critical steps and intermediates**

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. Standard test procedures should be provided where required.

3.2.P.3.5 Process validation and/or evaluation

This is one of the key sections; called as “Sterility Assurance Pack or Micro pack” This is one amongst the mandates of the USFDA for the sterile Manufacturing products. 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).

Information for terminal moist heat sterilization processes**3.2.P.4 Control of excipients****3.2.P.4.1 Specifications**

The details this section should possess includes

- Specification of the excipient
- Supplier Certificate of Analysis

3.2.P.4.2 Analytical Procedures

3.2.P.4.3 Validation of analytical procedures

3.2.P.4.4 Justification of Specifications

3.2.P.4.5 Excipients of human or animal origin

3.2.P.4.6 Novel excipients

3.2.P.5 Control of drug product

3.2.P.5.1 Specifications

3.2.P.5.2 Analytical Procedures

3.2.P.5.3 Validation of analytical procedures

3.2.P.5.4 Batch Analysis

3.2.P.5.5 Characterization of Impurities

3.2.P.5.6 Justification of Drug product Specification

3.2.P.6 Reference standards or materials

3.2.P.7 Container closure system

3.2.P.8 Stability

3.2.P.8.1 Summary of Stability studies and Conclusion

3.2.P.8.2 Post approval stability protocol and stability commitment

3.2.P.8.3 Stability Data

1. Formal Stability Studies

The results from long-term, accelerated and, when performed, intermediate studies undertaken on primary stability batches should be provided. Stability study reports should also be included.

If the analytical procedure listed in the stability protocol is different from the analytical procedure described in P.5 for the corresponding test.

2. Supporting stability studies

Data, other than those from formal stability studies, that support the analytical procedures, the proposed shelf life, and label storage statements can be provided.

Module 3.2.R Regional Information

To complete the regional section of Module 3 the applicant should refer to the appropriate Health Canada CTD Quality guidance documents.

Module 3.2.R.1 Production Documentation

R.1.1 Executed Production Documents

Copies of the executed production documents (English or French original or translated) should be provided for the batches used in the pivotal clinical and/or comparative bioavailability studies.

R.1.2 Master Production Documents

Copies of the drug product master production documents should be provided for each proposed strength, commercial batch size, and manufacturing site.

The details in the master production documents should include, but are not limited to, the following:

- a) special handling provisions relevant to the drug substance (e.g. antibiotics, teratogenic substances);
- b) precautions necessary to ensure product quality (e.g. temperature and humidity control, maximum holding times);
- c) dispensing, processing and packaging sections with relevant material and operational details;
- d) relevant calculations (e.g. if the amount of drug substance is adjusted based on the potency results or on the anhydrous basis);
- e) identification of all equipment by type and working capacity;
- f) process parameters (e.g. mixing time, mixing speed, milling screen size, processing temperature range, tablet machine speed);
- g) list of in-process tests (e.g. appearance, pH, potency, blend uniformity, viscosity, particle size distribution, LOD, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity);
- h) sampling plan with regard to the steps where sampling should be done (e.g. drying lubrication, compression):
 - i. number of samples that should be tested (e.g. blend drawn using a sampling thief from x number of different parts of the blender);
 - ii. frequency of testing (e.g. weight variation every x minutes during compression or capsule filling);

Module 3.2.R.2 Medical Devices

Module 4: Nonclinical Study Reports

Module 4 is not applicable for generic drug dossier it is only for new drug products

Module 5: Clinical Study Reports

Module 5.3.1.2 Comparative Bioavailability (BA) / Bioequivalence (BE) Study Reports

Module 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Module 5.3.6 Post Marketing Experience

Module 5.3.7 Case Report Forms and Individual Patient Listings

Canada Drug Approval Process

The approval of a new medication can take around 8-12 years and cost up to \$1 billion dollars

- Step 1: Research and Development
- Step 2: Patent Protection
- Step 3: Pre-clinical testing
- Step 4: Clinical Trial Application
- Step 5: Clinical Trials
- Step 6: Health Canada's Drug Review Process
- Step 7: Notice of Compliance
- Step 8: Drug Scheduling
- Step 9: Price Review
- Step 10: Advertising
- Step 11: Distribution
- Step 12: Listing on Provincial Formularies
- Step 13: Post-marketing Surveillance

GENERIC DRUG FILING IN EUROPE

The EMA defines a generic medicine as: a medicine that is developed to be the same as a medicine that has already been authorised (the 'reference medicine'). A generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s) as the reference medicine. However, the name of the medicine, its appearance (such as colour or shape) and its packaging can be different from those of the reference medicine ^[3].

Medicinal products are highly regulated in the European Union (EU) and are subject to a separate, complicated system of approval procedures. The marketing authorization procedure is applicable to European economic area (EEA) which includes 27 EU member states and the three EEA EFTA states (Iceland, Liechtenstein and Norway). Hence, EEA constitutes total 30 countries.

Module: 1¹⁷**1.0 Cover Letter**

The cover letter to the application should be included here. Where necessary, a "Notes to Reviewers" document could be provided as an Appendix to the cover letter, providing further information in order to facilitate navigation (e.g. on hyper linking, volumes presentation etc. For paper submissions, only the relevant cover letter for the Member State concerned /EMEA should be provided.

1.1 Comprehensive Table of Contents**1.2 Application Form**

- a. The European Medicines Agency under the centralized procedure or
- b. A Member State (as well as Iceland, Liechtenstein and Norway) under either a national, mutual recognition or decentralized procedure.

1.3 Product Information**1.3.1 SPC, Labelling and Package Leaflet****SPC:**

The Summary of Product Characteristics is a specific document required within the European Commission before any medicinal product is authorized for marketing.

The list of headings that organizes the information

- Name of the medicinal product
- Qualitative and quantitative composition
- Pharmaceutical form
- Clinical particulars
 - Therapeutic indications
 - Posology and method of administration
 - Contraindications

- Special warnings and precautions for use
 - Interaction with other medicinal products and other forms of interaction
 - Pregnancy and lactation
 - Effects on ability to drive and use machines
 - Undesirable effects
 - Overdose
- Pharmacological properties
 - Pharmacodynamic properties
 - Pharmacokinetic properties
 - Preclinical safety data
- Pharmaceutical particulars
 - List of excipients
 - Incompatibilities
 - Shelf life
 - Special precautions for storage
 - Nature and contents of container
 - Special precautions for disposal and other handling
- Administrative Data
- Marketing authorization holder
- Marketing authorization number(s)
- Date of first authorization/renewal of the authorization
- Date of revision of the text

1.3.2 Mock-up

A “mock-up” is a copy of the flat artwork design in full colour, providing a replica of both the outer and immediate packaging, providing a two-dimensional presentation of the packaging/labelling of the medicinal product. It is generally referred to as a “paper copy” or “computer generated version”.

1.3.3 Specimen

A “specimen” is a sample of the actual printed outer and immediate packaging materials and package leaflet.

1.3.5 Product Information already approved in the Member States

1.3.6 Braille

Applicants should address here the proposed implementation of the Braille requirement on the packaging of the medicinal product concerned, based on the principles set-out in European Commission guidance document. In addition, the Braille text (in normal font) which will be printed on the outer carton in Braille needs to be included in the outer carton product information templates (if applicable) and should be indicated with dots on the mock-ups (where applicable and feasible).

1.4 Information about the Experts

- The Quality Overall Summary
- A declaration signed by the experts in Module 1.4.
- A brief information on the educational background, training and occupational experience in Module 1.4 (CV of the expert)

1.5 Specific requirements for Different Types of Applications.

1.5.1 Information for Bibliographical Applications

1.5.2 Information for Generic, ‘Hybrid’ or Bio-similar Applications

A ‘generic’ of a reference medicinal product

1.6 Environmental Risk Assessment

1.7 Non-GMO

Applications for marketing authorization’s for medicinal products which do not contain GMOs (Genetically Modified Organisms) should include in Module 1 an indication of any potential risks

presented by the medicinal product.

1.8 Information relating to Pharmacovigilance

1.8.1 Pharmacovigilance System

1.8.2 Risk-management System

Module 2 - Common Technical Document Summaries ^[18]

2.1 CTD table of contents

2.2 CTD introduction

2.3 Quality Overall Summary

2.4 Non-clinical Overview

2.5 Clinical Overview - not required for generics

2.6 Non-clinical Summary – not required for generics

2.7 Clinical Summary

2.7.1 Summary of biopharmaceutics and associated analytical methods

2.7.2 Summary of clinical pharmacology studies

2.7.3 Summary of clinical efficacy

2.7.4 Summary of clinical safety

2.7.5 Synopses of Individual Studies

In US and EU the module 2 is same only the difference is batch size, storage conditions, limits as per European pharmacopeia is different.

Module -3 (Quality)

3.1 MODULE 3 TABLE OF CONTENTS

3.2 BODY OF DATA

3.2.S DRUG SUBSTANCE

In 3.2.S.2 Manufacture section, 3.2.S.2.3 to 3.2.S.2.6 is restricted part of ASMF

3.2.P Drug Product

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

3.2.A.2 Adventitious Agents Safety Evaluation

3.2.A.3 Excipients

3.2.R REGIONAL INFORMATION Validation of the process

3.3 LITERATURE REFERENCES

MODULE -4 Non Clinical Study Reports

For generics it is not applicable

Module -5 Clinical Study Reports

5.1 MODULE 5 TABLE OF CONTENTS

5.2 TABULAR LISTINGS OF ALL CLINICAL STUDIES

5.3 CLINICAL STUDY REPORTS

5.3.1 Reports of Biopharmaceutical Studies

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

5.3.3 Reports of human pharmacokinetic(PK)studies

5.3.4 Reports of human pharmacodynamic(PD)studies

5.3.5 Reports of efficacy and safety studies

5.3.6 Reports of post-marketing experience

5.3.7 Case report forms and individual patient listings, when submitted

5.4 LITERATURE REFERENCES

Generic drug approval in Europe¹⁹

For marketing authorization of the generic medicinal product in Europe, the applicant should submit abridged application to the relevant authority. The marketing authorization is done by the following types of procedures. They are:

1. Centralized procedure

2. National procedure
3. Decentralized procedure
4. Mutual recognition procedure

Centralized procedure¹⁹

The centralized procedure was enforced in the EU in 1995.

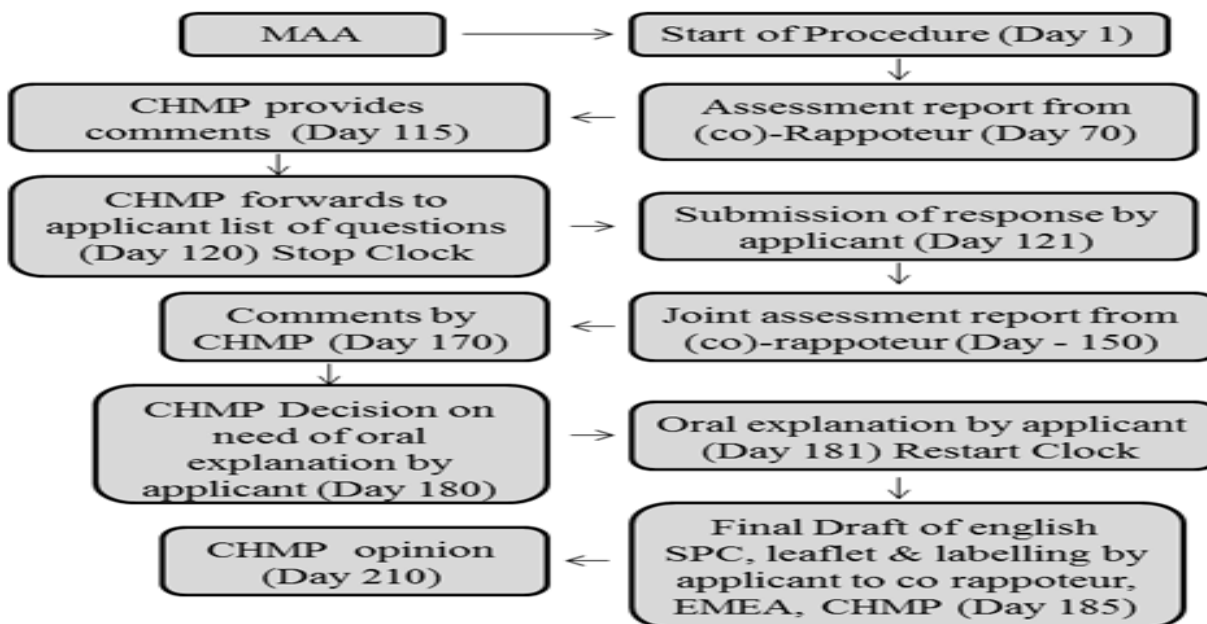


Fig. 6: Centralized procedure¹⁹

National procedure

The Timeline for this procedure is 210 Days.

The mutual recognition procedure

The mutual recognition procedure was enforced in the EU in 1995.

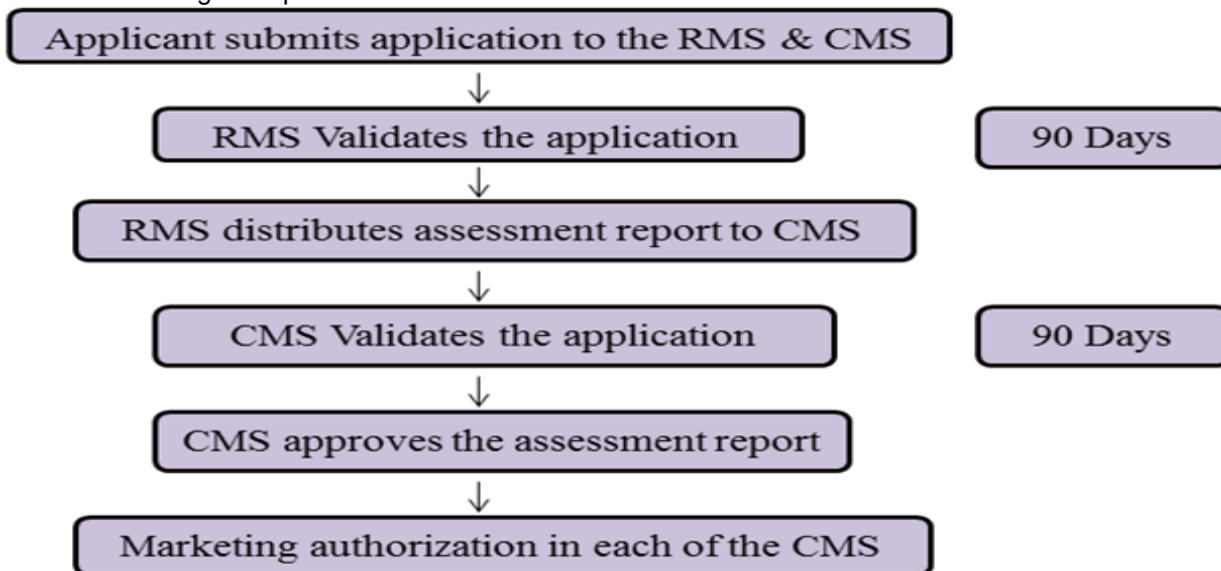


Fig. 7: Mutual Recognition Procedure²⁰

Decentralized procedure

The new Decentralized procedure was enforced in the EU in 2005.

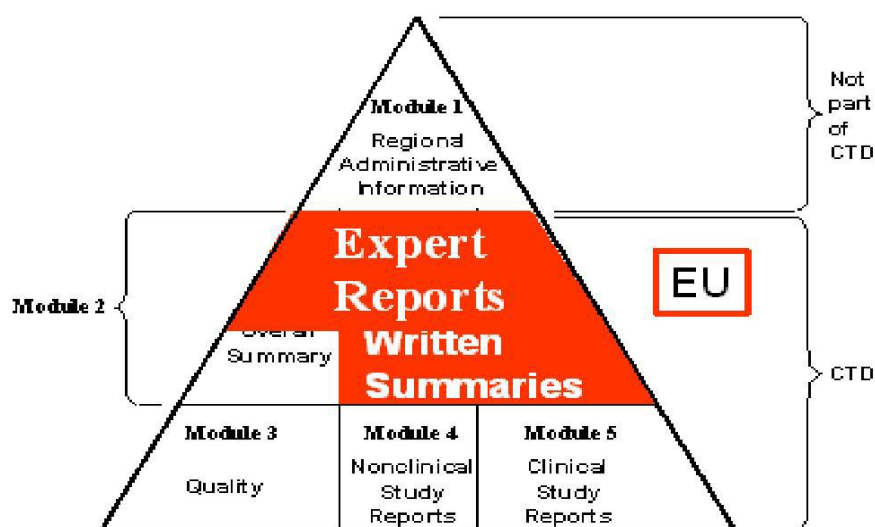
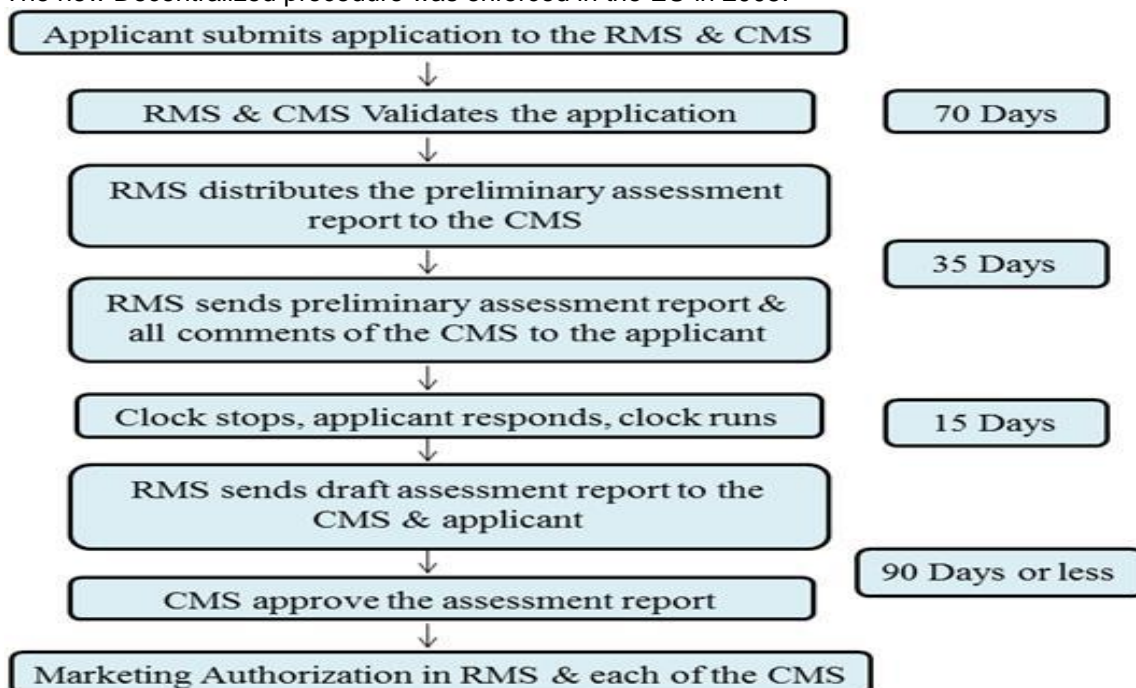


Fig. 8: Decentralized procedure²¹

Table 8: Comparison of generic drug dossier submission in US, Europe and Canada²²

Requirements	US	EUROPE	CANADA
Agency	One Agency USFDA	Multiple Agencies <ul style="list-style-type: none"> • EMEA • CHMP • National Health Agencies 	Therapeutic Products Directorate (TPD) of the Health Products and Food Branch (HPFB), Health Canada
Registration Process	One Registration Process	Multiple Registration Process <ul style="list-style-type: none"> • Centralized (European) 	One Registration Process

		Community) <ul style="list-style-type: none"> Decentralized (At least 2 member states) Mutual Recognition (At least 2 member states) National (1 member state) 	
Application	ANDA	MAA	ANDS
Stability data	The stability data for accelerated studies are submitted for three months at the time of original submission.	The stability data for accelerated studies are submitted for complete 6 months at the time of original submission.	The stability data for accelerated studies are submitted for complete 6 months at the time of original submission.
Approval time	18 months	12 months	2 years
Pharmacopeias	US pharmacopeia	BP/Ph. Eur.	BP/Ph. Eur./USP
Batch size	Min of 1,00,000 units	Min of 1,00,000 units	2 pilot scale batches
Process Validation	Not required at the time of submission	Required	Not required at the time of submission
Post-approval changes	Post-approval changes in the approved drug: <ul style="list-style-type: none"> <input type="checkbox"/> Minor changes <input type="checkbox"/> Moderate changes <input type="checkbox"/> Major changes 	Post-variation in the approved drug: <ul style="list-style-type: none"> <input type="checkbox"/> Type IA Variation <input type="checkbox"/> Type IB Variation <input type="checkbox"/> Type II Variation 	Post-approval changes in the approved drug: <ul style="list-style-type: none"> <input type="checkbox"/> Minor changes <input type="checkbox"/> Moderate changes <input type="checkbox"/> Major changes

Table 9: Comparison based on Modules in US, Europe and Canada

Module 1:Regional information		
US	EUROPE	CANADA
i. Administrative information is different i.e. cover letter, forms (356h), application information, field copy certification, debarment certification, financial certification, Patent information and exclusivity18.	i. Administrative information such as cover letter specified for the particular country, application form applicable in that country, exclusivity statement, proof of payment to clinical investigators, proof of establishment of the applicant in EEA.	i. Administrative information Correspondence Table of Contents (M1 to 5) Administrative Information Product Information Health Canada Summaries Environmental Assessment Statement Regional Clinical Information Clinical Trial Application and Clinical Trial Application- Amendment Specific Requirements
ii. The paper size for the submission is Letter size (8.5x11 inches) with font size 12 in times new roman format. The tables and figures have small font size i.e. 8 to 10.	ii. A4 (8.27x11.69inches) paper size is used for the dossier preparation with font size 12 in times new roman format.	ii. The paper size for the submission is Letter size (8.5x11 inches) with font size 12 in times new roman format. The tables and figures have small font size i.e. 9.
iii. Package inserts are provided for drug product in labelling.	iii. SPC (summary of product characteristic) is provided about the drug product in labelling.	iii. Package inserts are provided for drug product in labelling.
iv. Proposed Labels and cartons with proper dimensions similar to that of the RLD labels are provided.	iv. Mock ups and specimens of labels and cartons sent with the application as appropriate. Braille is used for the labelling conditions on the labels.	iv. Proposed Labels and cartons with proper dimensions similar to that of the RLD labels are provided.
v. Request for waiver of in-vivo BE studies is provided in the module 1.	v. Request for waive is not provided in the module 1.	v. Request for waiver of in-vivo BE studies is provided in the module 1 in module 1.6.
vi. Annotated draft labeling (side by side) for labels and cartons compared with the RLD with proper annotation is provided.	vi. No annotation (side by side) for labelling is provided. Everything is provided in the SPC and package inserts.	vi. Annotated draft labeling (side by side) for labels and cartons compared with the RLD with proper annotation is provided.
vii. The EAS (Environment Assessment Statement) for categorical exclusion certification in compliance with the law of EPA of US is provided.	vii. Environ risk Certification ²¹ is given with the information for GMO or Non - GMO. The fresh/new certificate is provided.	vii. EAS is required for new substances in products regulated under the F&D Act as per the New Substances Notification Regulations

		(NSN) of the Canadian Environmental Protection Act (CEPA)
viii. Risk management Plans section is for the post marketing surveillance and controlling the adverse effects of the drugs by proper management. This is the part of Clinical Trial Phase IV.	viii. A separate additional section is provided for the pharmacovigilance system for surveying and controlling the post approval undesired effects of the drug.	viii. Risk management plans or their equivalent section is for Pharmacovigilance Information.
Module 3		
Module 3.2.R (i) The executed batch records for manufacturing and packaging are provided in Module 3.2.R for only single batch.	Module 3.2.R (i) The three executed batch records for manufacturing and packaging for process validation schemes are provided in Module 3.2.R.	Module 3.2.R (i) The two executed batch records for manufacturing and packaging are provided in Module 3.2.R.
(ii) Information on components including the name and address of the supplier or manufacturer of the raw material, package material etc provided in the 3.2.R.	(ii) Information in components employed in the drug product formulations is generally not provided in the module 3.2.R	(ii) Information in Yearly Biologic Product Report (YBPR), provided for BGTD only, is to be provided in module 3.2.R
(iii) Letter of Access is not mentioned in 3.2.R.	(iii) Letter of access to Active substance master file of drug substance is provided for the agency.	(iii) Letter of Access is not mentioned in 3.2.R.
(iv) TSE and BSE certificates are not attached in this section whereas submit in DMF.	(iv) TSE and BSE certificates are attached for drug substance and excipients.	(iv) TSE and BSE certificates are attached for drug substance and excipients.
(v) Certificate of suitability (CEP certificate) is not applicable.	(v) The latest Certificate of suitability (CEP) obtained from the EDQM Europe for each drug substance and excipients are attached.	(v) Certification of Suitability to the Monographs of the European Pharmacopoeia (CEP) for the Quality of Medicines and Healthcare.

6. CONCLUSION

The generic drug filing in the United States, Europe & Canada are the most demanding in the world. The primary purpose of the rules governing medicinal products in US, Europe & Canada is to safeguard public health. It is the role of public regulatory authorities to ensure that pharmaceutical companies comply with regulations. There are legislations that require drugs to be developed, tested, trialed, and manufactured in accordance to the guidelines so that they are safe and patient's well - being is protected.

CTD provides a globally harmonised format that is accepted in many regions, avoiding the need to compile different registration dossiers for different regulatory authorities. The primary purpose of the rules governing medicinal products in US & Europe is to check whether drugs are manufactured in accordance to the guidelines so that they are safe and patient's well - being is protected. Countries have different standards; there are high registration costs and long timelines for registration of generic drugs. This may account for the low market share of generics in Europe as compared to USA and Canada.

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