Vol 5|Issue 3| 2015|308-320.

International Journal
of
Pharmacy Review & Research
www.ijprr.com

e-ISSN: 2248 – 9207
Print ISSN: 2248 – 9193

REGULATORY APPROVAL OF GENERICS IN CANADA MARKET

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ABSTRACT

The present thesis determines the regulations and regulatory approval process of generics in Canada. Canada is the largest individual market in North America. It is the 8th largest market in the world and in the pharmaceutical sales the Canada country is containing 2.5 percentage of sales in global market. In the 2009-2013 recent survey Canada is the 7th fastest growing country in the north America most of the company undertaking research and development (R&D) and to develop the new or improved patent therapies and other developing taking on other bio-equivalent and subsequent entries of biologics and generics it will taking a shape. Most of the brand name products will be account for 76 percentage in Canada country and 37 percentage of prescriptions and rest of the account in generics. In the activity of research and development the pharmaceutical companies on Canada can expenditure $ 1 billion since 2011 then from 2001-2012 fallen by 15.6 percentage. Then for regulatory requirements for registration of generics can be authorized by national association of pharmacy regulatory authorities (NAPRA) and then prescription drugs are evaluated by Canadian generic pharmaceutical association (CGPA), Health Products and Food Branch Inspectorate (HPFBI) . There are different requirements for registration or approval of product in Canada for the regulatory agencies requires the pharmaceutical dossier to get an approval to the market drugs. The dossier document can represents the technical aspects of a particular drug formats is explain elaborately at a certain manner as like about the administrative information, chemical manufacturing control, non-clinical reports, and clinical reports, approval forms attached at certain manner. The pharmaceutical companies are prepare dossier at certain formats like common technical document (CTD) / electronic technical document (ECTD) / NON-CTD (country on specific guidelines). Some of the CIS countries like fallow their own dossier formats.

Key words: Generic, Health Products and Food Branch Inspectorate (HPFBI), National association of pharmacy regulatory authorities (NAPRA), common technical document (CTD) / electronic technical document (ECTD) / NON-CTD (country on specific guidelines), CIS countries.

INTRODUCTION

Canada is the commonwealth and largest individual growing market in the north America. In these country the drug regulations and registration is a system that fallow on all pharmaceutical products to maintains the pre-marketing evaluation, marketing authorization, and post-marketing review to ensure that they conform to required standards of quality, safety and efficacy established by Canada regulatory authorities. In these country most of the unique pharmaceutical companies maintains some regulatory process certain programming manner as like representing on pharmaceutical dossier on generic drugs to the government authorities to get a approval at certain format manner are elaborately explained below [1].

Country profile

Regulatory authority: National Association of pharmacy regulatory authorities (NAPRA) 1995, Health Products and Food Branch Inspectorate (HPFBI) 1986.
National Language: English
Government: The bilingual government of du Canada word mark
Capital: Ottawa
Currency: Canadian dollar (CAD)
1 CAD = 54.69 Indian rupees (on date of completion)

Pharmaceutical sector in Canada

In Canada the pharmaceutical sector is the one of the most unique and innovative pharmaceutical industries in Canada. Then most of the composed companies are

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developing and manufacturing innovative medicines and generic pharmaceuticals, as well as over the counter drugs products. In these sector made up of a number of sub-sectors that services different market segments and these include brand- name pharmaceuticals companies, generic drug firms, biopharmaceutical small and medium sized enterprises (biopharmaceutical sems) and contract service providers (csps) [2].

Structure and size of the pharmaceutical industries in Canada:

Canada is the one of the largest growing individual market in north America. In the sales of the pharmaceutical products in Canada have a 2.5 percentage has been share in the global market making by these country. It is the 8th largest market in the world it consists 2.2 percentage compound annual growth on over the period between 2009-2013.

The Canada is the 7th fastest growing country in the market globally under (IMS Health pharmafocus in 2017). In these country the companies undertaken for the research and development (R&D) and to development of new or improved patented therapies and while other development of bio-equivalent copies of certain generic innovative drugs once patent expires. An emerging field of biologics and generic subsequent entry of biologics (SEBS) and generics under for subsequent entry of generics (SEBG) is also taking under shape at certain manner by the companies. The brand name of the products account for 76 percentage of Canadian sales and the reaming 37 percentage for the prescription under drugs and the generics account for the rest. In the 2.13 the manufacturing portion of the sector employed 27,000 people and over the last 10 years employment is has been increasing by 1.6 percentage in the industry is clustered mainly in the metropolitan areas of Vancouver, Montreal and Toronto.

The growth of the pharmaceutical industries was increasing in most of the recent years on the most of the working staff will be increasing day by day on these pharmaceutical industries and also economic growth on increasing to maintains at certain manner [3].

Research and development Activities in Canada

In the activity of research and development activities on canada consisting the most of the pharmaceutical companies are doing the business on total expenditure on research and development by the pharmaceutical companies has fallen below on the 1$ billion since 2011. Initially from the 2001 to 2012 industry research and development spending has fallen by 15.6 percentage most over the industries changing business model more on the research and development is being conducted on externally and through partnerships. In these includes investments in seems, venture funds and work with in Canada country growing the CSP sector. On the recent survey by RX&D and KMPG highlights many of these new investments, that indicating an additional research and development (R&D) and expenditure of the mostly represents on $ 221 million in 2012. In the pharmaceutical industry is the second after and the information technology (IT) sector in research and development intensity then on the twenty two pharmaceutical and biotechnology companies are listed in research enforces on top 100 companies are corporate and R&D spenders on 2013 in Canada. On research and development costs per drugs averaged on US$ 605 million on over between 12- 13 years on tufts center for the study of drug development. Full of costing including amortization of research failure and opportunity cost of capital at arises average costs on significantly. A generic drug may take at on 2 to 3 years and requires $3 to $ 10 million of research and development to develop and prove equivalency with original drug. The overall view on development on R&D on from 2001- 2012 is viewed on table reference on given below at table 1[4].

GENERICS

The generic medicine is a medicine that is developed to be the same as a medicine that has already been authorized at the reference medicine. The generic medicine is marketed in compliance with on international patent law and it is identified either by its internationally approved and non- proprietary scientific name (INN) or by its own brand name. The generic drug provides the maintains of quality, safety and efficacy as the original on name of the product undergoes strict scrutiny before its license is given market approval by the Canadian or national medical authorities and the various definition on generics on Canada, USA, Europe are given below reference at table 2 .

INTRODUCTION

The generic drug contains a drug product which is comparable to a reference (brand) listed drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use. The generic drug is a typically be granted marketed that are authorization after the innovators patent on the drug has expired in the market. The generic contains on various structure on changes of position atomic structure on a certain generic product the internal structure of generic will given below reference at figure 1 [5].

Process of development generic product in Canada
About on Generic product

The generic drug product is produced based on the chemical synthesis changes of the position of generic on organic structure and these are far smaller size contains <500 Daltons (Da) and the molecular weight will be at 1000 mol.wt and it will be the self contained consisting of the organic molecules as well defined in physicochemical properties. The generic drugs usually stable and single entity and high chemical purity and it standards well established on identical copy can be made at the administered through at different route of administration and the rapidly enters on the systemic circulation through blood capillaries and to distribution to any combination of organ / tissue often on specific toxicity and non-antigenic [6].

Manufacturing of generics

The manufacturing of generics considering certain following points on production of generic medicine:

- The generics is completely is characterized on the analytical methods.
- The generics products are easy to purify, less costs and cheap.
- In these products the contamination can be generally avoided and easily detectable and removable.
- It is not affected by at slight changes in production process and environment.
- On the generics the production products will be reproducibility can be easy to establish.

Clinical development on generics

In Canada the clinical development on generics are more invested by the pharmaceutical companies and maintains certain limitations on generic products.

- Limited clinical activities, and often on phase 1 pharmacokinetic/ Pharmacodynamic studies.
- On generics to getting short timeline for approval.
- On development of generics the clinical trials on Canada the pharmaceutical companies invests costs on usually up to 5 millions $.
- At on the enrolment of around 20-100 subjects [6].

Development stages of generics

The development of generics on the Canada the pharmaceutical companies are the initially to integrating the drugs will on production. Then changes on production process on packing, or on the dissolution and towards on bioequivalence, bioavailability studies, pharmacokinetic studies. Pharmacodynamic studies, clinical phases is the major plays important role on the generics. The development of generics will be taken at certain stages represent on flow chart given below at a understand manner reference at figure 4 [7].

Development challenges

In these development challenges is the way to get the information from the obtain components of the authorized drug is already approved product presence in the Canada market and it is multiple batches on the authorized new product on spanning a number of years and it can be helpful during to that characterizes on that process.

These are the source of development changes on new generic drug and between already manufactured generic products are presence on the Canada market are given below:

- Use of different terminology
- Different operation conditions
- Using different reagents and standard reagents
- Using different binding and evolution conditions

These are the field of generics presents on several important challenges are including to development of new generic product in Canada market:

- On certain verification of the terminology.
- The interchangeability between new generic product at on the authorized product presence in the Canada market.
- Changes on the regulatory framework.
- The possibility of unique naming differentiates from the various generic products.
- The maintains of intellectual property rights and public safety on the generic products [7].

Patent study

On patent studies in Canada the pharmaceutical generic products are consisting patent is certain period contains 20years term from the filling application date in Canada. In these country the patent term extensions as proposed at certain meant to provide up to 5.5 years of additional exclusivity for a generic drug time period a patent protected products is on the market has been shortened by the lapse of time between the filling of a certain patent and the grating of Canada market authorization by health Canada. Then elaborately explanation on patent exclusivity of Canada, Australia, and United Kingdom countries are given below reference at table 3[8].

Market for by drug class

Generics market value $379 CAD million at on 2013. On the generic products the global generics market is further segmented into recombinant on proton pump inhibitors like (omeprazole) and the antipsychotic drugs like (olanzapine), antiseizure or anticonvulsants like (Topiramate).

Human growth the generics and glycosylated proteins like (erythropoietin, monoclonal antibodies, and follitropin), and recombinant peptides (glucagon and calcitonin). In 2013 the generics are like anti bodies and omeprazole products like will account for 66 percentage of the global generics market. The generic human growth of the generic submarket will be the slowest-growing of the leading generic market sectors. The generic market's are several leading segments currently are given below:

- Bosulif – A kinase inhibitor for chronic myelogenous leukemia (CML).
- Omeprazole.
- Duavive.
- Elelyso.
- Harvoni.
- Topiramate.
- Olanzapine.

On all segments under the product category, the antibodies and proton pump inhibitors segment, anti diabetic segments is the fastest-growing segment at an estimated at on economic generic growth in Canada (CEGA) at on more than 20% from 2013 to 2018. On application anti-diabetic and anti-bodies is the largest and fastest and growing segment and account for a share of 30% of the global generics market and Steps involved in the development and Marketing of generics are given below reference at figure 2 [9] [10].

Objectives

- To understand quality requirement for e-CTD, CTD submission.
- To study about the generic drugs market in Canada.
- To understand submission and registration approval process with in regulatory authorities in Canada.
- To list out of administrative requirements for document to registration of drug product in Canada.
- To understand drug regulation in Canada.

Research methodology

The present paper deals with the following aspects:

Study parameters

The study parameter was conduct in the following below consideration on present thesis:

- To explanation about the generics.
- To represents about the market analysis of generics in Canada.
- Role of Canada regulatory authority in registration of generics.

To provide a complete picture of the registration procedure applicable to generics drugs in Canada .The regulatory bodies in the country is at the helm of the affairs pertaining to the affairs of the drug registration approval, denial and any other further works carried out by such organization. The correct understanding of the functioning of regulatory body helps in providing a vivid picture to the applicant and helps in reducing lot of time and money. Hence to provide a vivid picture the functioning of regulatory body is covered.

Regulatory submissions

- Types of Registrations and application forms required for the countries.
- Timelines involved in the approval.
- Fee Requirements.
- The various documents need to be submitted along with the application forms for specific manufacturing and import in Canada.

The data for the compilation is mainly sourced from websites of various regulatory bodies of Canada, Guidance documents and guidelines issued by the regulatory bodies of Canada, Journals and published articles related to regulatory strategies, the most critical regulatory concerns that drive the regulatory submission in Canada.

Generics Drug Registration

Like all other drugs, a Generic medicine requires to receive a marketing authorization before it can be marketed. The marketing authorization is granted by different regulatory authorities in different countries. The regulatory framework in Canada regarding manufacturing process and quality aspects for generics involves a vast process. The following are the guidelines involved in the approval process of recombinant pharmaceutical products.

Institutions and Committees responsible for Generics Approval in Canada:

- Health Products and Food Branch Inspectorate (HPFBI)
- Therapeutic product directorate (TPD)
- Scientific Affairs committee (SAC)
- Provincial Regulatory Working group committee (PRWGC)
- Canadian expert drug advisory committee (CEDAC)
- Intellectual Growth Committee (IGC)
- Market Growth committee (MGC)
- Industry Practices Review Board-Quebec committee (IPRBQC)
- Subsequent Entry Biologics Committee (SEBC)

The HPFBI is the national regulatory authority in Canada, headed by the Therapeutic product directorate (TPD) evaluates safety, efficacy and quality of generic drugs in the country. PRWGC, CEDAC and IGC are constituted at the central level by TDP and MoEF. SEBCs work in the area of generics; Canada Biotechnology coordination Board (CBC) are responsible for monitoring the activities related to generics in national level. PRWGC has advisory in function while CEDAC and IGC are involved in regulatory functions and about working on committee legislation will be given below reference at table 4 [11].

Procedure for Marketing Authorization of Generics in Canada

The development of generics involves a stepwise approach of optimizing the production process, comparability exercise for characterization of the product (physicochemical as well as biological) followed by pre-clinical and/or clinical studies. To develop, a generic manufacturer will need to first identify a marketed generic product to serve as the reference generic product. Then a detailed characterization of the reference generic product will be performed. The information obtained from the characterization of the reference generic product will be utilized to direct the process development of the generic product and comparative testing to demonstrate bioequivalence between the innovating generic product and the reference generic product [12].

Research and development activities on generics

The product development for generics initiates with the constitution of HPFBI in an organization where the product is being manufactured. HPFBI is responsible for looking after all the research activities in an institution.

Constitution of HPFBI

The HPFBI shall have the following members:

- Head of the organization or his designate (a suitable senior officer) as the Chairperson
- Three or more scientists engaged in bioequivalence work or molecular biology with at least one outside expert in the relevant discipline.
- A member with medical qualifications – generic safety Officer (in case of work with pathogenic agents/large scale use).
- A nominee of DBT.

The aspects to be reviewed by HPFBI broadly include scientific considerations and availability of appropriate facilities. In addition, DBT nominee is also expected to review the organizational set up, facilities, and status of other approvals required/obtained etc. of generic research projects on a case-to-case basis. After setting up HPFBI, for developing a product generic material is required and this is imported for R&D purpose and for license. All applicants seeking the approval of HPFBI/ TPD/SAC/PRWGC are here by directed to strictly follow the step-wise procedures outlined in the five protocols as applicable in the respective cases. The product where the end product is generics has the potential for propagating/replicating in the environment and therefore needs a higher level of regulation as compared to products derived from generics where the end product [13].

Preclinical evaluation of generics

In Canada the preclinical evaluation conducting after the completion of research work, preclinical studies are conducted. For conducting the preclinical studies, an organization has to obtain permission from HPFBI recommended by TPD (Form of clinical trial site information form).

As per guidelines for preclinical and clinical evaluation of generics, diagnostics and other biological the abridged pathway for preclinical and/or clinical testing of a similar generic depends on establishing comparability with the reference innovator product as well as establishing the consistency in its production and purification. The approach to be adopted should be fully justified in the pre clinical overview, wherein each applicant must submit the following clinical information:

- Known / proposed clinical use of the product in Canada, any specific indications proposed to be targeted and consideration of age, sex, pregnancy, lactating, children etc.
- Dosage schedule including quantity of each dose, number of doses/day, frequency and intervals and total duration of treatment
- Mode of administration e.g. pre filled syringe
- Details of final formulation including adjuvant, additives etc.,
- Information about diluents, if any.
- Available toxicity data in human / animals on innovator recombinant product and toxicology data of adjuvant and additives as applicable.

The applicant is also required to furnish information about the proposed test site and personnel to be involved in conducting these studies at the test site e.g. study director, principal investigator, pathologist, other investigators and quality assurance officer. The statutory approvals from HPFBI and TPD must be submitted, as the case may be. The studies should ideally be conducted as per GLP and the applicant should inform about the status of accreditation of test site, if any. Preclinical studies should be conducted with the final formulation of the generic intended for clinical use, unless otherwise justified. Accordingly, the data requirements for preclinical approval of a generic are as follows:

- Manufacturing process considerations
- Product Characterization
- Pharmacological characteristics
- Formulation and Stability studies
- Preclinical evaluation
- Immune responses in animals
- Efficacy of the product
- Archiving of data

The data requirements for review of manufacturing process at preclinical submission stage includes a complete description of the manufacturing process from development and characterization of generic product description, molecular biology details with including origin of gene, gene sequences, stability of clone, fermentation, harvest, excipients, formulation, purification, primary packaging interactions (if different from reference Generic), standardization of fermentation/production procedures ate to be provided for TPD. All the data up to preclinical evaluation for a period of at least five years should be archived by the applicant after marketing approval by competent authority in Canada or as per HPFBI, USFDA, ICH, EMA requirements. The site of archiving should be indicated in the study protocols and reports [14, 15].

Preclinical Studies

Preclinical studies are conducted in animals prior to clinical trials in humans and the report is to be submitted to TPD for approval. These studies are conducted with all the proper GLP facilities in the accredited laboratories. The animal studies are conducted in an accredited laboratory.

Pre-clinical studies include

A. Animal Toxicology Data (Non-Clinical)

1. General principles:

i. Systemic Toxicity Studies: Single-dose toxicity studies & Repeated-dose systemic toxicity studies ii. Male Fertility Study

iii. Female Reproduction And Developmental Toxicity Studies: Female Fertility Study (Segment I), Teratogenicity Study (Segment II) , Perinatal Study (Segment III)

iv. Local toxicity

v. Allergenicity/Hypersensitivity

vi. Genotoxicity

vii. Carcinogenicity

viii. Animal toxicity requirements for clinical trials and marketing of a generic drug.

ix. Number of animals required for repeated-dose toxicity studies.

2. Laboratory parameters to be included in toxicity studies like Haematological, Coagulation, Urinalysis parameters, Blood Biochemical Parameters like Glucose, Cholesterol, Triglycerides, Cholesterol (non-rodents only), Gross and Microscopic Pathology.

Animal Pharmacology (Non-Clinical)

- **Specific Pharmacological Actions** - Demonstrate the therapeutic potential for humans.

- **General Pharmacological Actions** -Essential Safety Pharmacology
- Follow-up and Supplemental Safety Pharmacology Studies
- Conditions under Which Safety Pharmacology Studies Are Not Necessary.
- Timing of Safety Pharmacology Studies In Relation To Clinical Development.
- Application of Good Laboratory Practices (GLP) [16].

Preclinical study reports

The final report of the study should reflect all the issues approved in the protocol and the following additional sections/documents:

1. List of studies completed and deviations, if any from the approved protocols
2. Dose calculation for conduct of safety studies
3. Study reports (Each study report would reflect all the issues approved in the protocols). In addition the following to be included:
   - HPFBI approval of protocol and test centre
   - TPD approval of report
   - IAEC approval for animal use and for the procedures
   - Quality assurance statement
   - Signatures of study director and all investigators who were involved in the study
   - All quality analytical reports on the test material and vehicle
   - Animal feed and animal health certifications
   - Protocol deviations if any
   - Discussion on the results
   - Individual animal data, summary data and any other data like computer analysis outputs etc
   - Conclusion
4. Address and accreditation status of the labs where these studies were conducted.

Data obtained from pre-clinical studies is submitted clinical site form to TPD, CEDAC. After thorough verification, CEDAC recommends to TPD for clinical trial permission. The documents to be submitted include: Preclinical study report and application for conducting clinical trials in Canada clinical site application to TPD [17].

Clinical studies

Clinical studies (trials) are usually performed in human beings to determine the safety, efficacy, risks and optimal use of the drug and/or its benefits and clinical studies to be conducting in clinical trials in phases I, II, III, IV are given below at table 5.

Phases of clinical trials

These clinical trial studies are conducted in 4 phases are given below:

1. Phase I-Human Pharmacology (determine safety)
2. Phase II-Therapeutic Exploratory Trials (determine whether the drug works)
3. Phase III-Therapeutic Confirmatory Trials (determine how effective the drug is compared to currently available effective drugs.)
4. Phase IV-Post Marketing Trials[18, 19]

Documentation for approval of clinical trials

All the data requirements are submitted for the approval of clinical trials along with the clinical trial application. The data is submitted at every phase of clinical trials for approval in the format as per HPFBI, Guidance for Industry:

SECTION A: General Information

SECTION B: Chemistry Manufacturing Control (Module 3)

SECTION C: Nonclinical Data (Animal Pharmacology and Animal Toxicology)

SECTION D: Proposed Phase I, II & III Studies

A clinical trial application utilizes:

- Clinical trial application form accompanied by documents pertaining to chemical and pharmaceutical information, animal pharmacology, toxicology data and clinical pharmacology data.
- Summary of relevant pre-clinical safety information,
- Investigator's Brochure,
- Trial protocol(study synopsis),
- Case report form(CRF),
- Ethics committee clearance,
- Copies of the informed consent documents (patient information sheet, informed consent form etc.),
- Investigator's undertaking.
- Trial's regulatory status of the trial in other countries must be reported.

After the completion of clinical trials, study report (certified by principal investigator) is also submitted to TPD for obtaining permission to market the drug. The data required will depend upon the purpose of the new drug application. The number of study subjects and sites to be involved in the conduct of clinical trial will depend upon the nature and objective of the study.

The submission must be in 2 hard copies and 2 soft copies i.e. CD's (PDF format) with document number, name of the firm, date of submission etc., Manufacturer should preserve/maintain one hard copy and soft copy of submitted documents in his/her safe custody for any future reference, if required and the registration process for clinical trial in Canada was given below refer figure 3.

Preparation of documents

- Collection of data related to studies
- Compilation of data as per respective forms.
- Review, filing and submission of data to TPD.

After acquiring approval of clinical studies, the drug can be manufactured and for this it requires manufacturing license. The manufacturer has to seek permission from licensing authority to obtain license. Then the drug is manufactured using proper GMP facilities in a plant followed by inspection of HPFBI. Later it is commercialized by attaining market authorization.

The Licensing Authority reserves the right to reject any data or any document(s), if any data or contents of such documents are found to be of doubtful integrity [20].

Marketing Authorization of Generics in Canada

The submission for marketing authorization of generics follows the format of "HPFBI, TPD Guidance for industry" in Canada. HPFBI prescribes information to be submitted for Drugs Approval (Market Authorization) of generics in the following format to simplify the submission requirements:

Module I: Administrative/Legal Information
Module II: Summaries
Module III: Quality Information (Chemical, Pharmaceutical and Biological)
Module IV: Non-Clinical Information
Module V: Clinical Information

The data is submitted to TPD in the above format. TPD reviews and if gets satisfied, approves a similar biologic for marketing. During marketing phase, if any queries or complaints or changes were been found this is to be reported to TPD immediately in the Post-Marketing Phase.

Post-Approval changes

For Generics, it is said that the process defines the product. For any change made in post market authorization, sponsor needs to assess the change for its potential to have an adverse effect on the identity, strength, quality, purity, or potency of a generic product as these factors may relate to the safety or effectiveness of the product and avail it to TPD. In Canada, as elaborated in HPFBI guidance document (CGPA/1108, ver. 05, Feb 2008), depending upon the impact of the change, application for a generically an generic product has to be filed with HPFBI in the form of periodic safety update reports (PSURs) with requisite supportive documentation. Data requirements to be included in the submission package for Level I and Level II Quality changes

- A covering letter (including a list of changes describing each in sufficient detail to allow for a quick assessment as to whether the appropriate reporting category has been used).
- A side-by-side comparison of the previously approved and the changed information.
- An electronic or hard copy of the Quality Overall Summary.

Though generics are not new drug products, their risk will be similar to reference generic and hence it is important to submit the Risk Management Plan (Includes Pharmacovigilance plan, Adverse Drug Reaction (ADR) Reporting, Post Marketing Surveillance) to monitor and detect both known inherent safety concerns and potential unknown safety signals that may arise from the similar generic. The reference generic shall be maintained throughout the life cycle of the product [21].

Table 1. Total Canadian R&D expenditures from 2001-2012

S.no	Year	Expenditures (in $ billions)
1.	2001	1.06
2.	2002	1.20
3.	2003	1.19
4.	2004	1.17
5.	2005	1.23
6.	2006	1.21
7.	2007	1.33
8.	2008	1.31
9.	2009	1.27
10.	2010	1.18
11.	2011	0.99
12.	2012	0.89

Table 2. Definition of generics

Canada	United States	Europe
As per the Canada the generics guidelines, generic includes: Generic drug is "a drug product which is comparable to a reference (brand) listed drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use" The generic drug is a typically be granted marketed that are authorization after the innovators patent on the drug has expired in the market.	In the U.S. the generic drug is the same as a brand name on drug maintains dosage, safety, performance, and on intended use. On before approving a generic drug product, the FDA requires many rigorous tests and procedures to assure that is the generic drug can be submitted for the brand mane drug. The FDA bases evaluations of substitutability or on the therapeutic equivalence of generic drugs on the scientific evaluations on law of a generic drug product and must contain the identical	A generic medicinal product it has the same qualitative and quantitative composition in the active substances on the same pharmaceutical forms as the reference on generic medicinal products, are those bioequivalence with reference on medicinal products has been demonstrated on appropriate bioavailability studies on a certain generic copies can only be an marketed after the originators patent protection and are marketing exclusivity has be expired.

	amounts of the same active ingredients as the brand name of product. The drug evaluated as it can be expected to have an equal effect and no difference when on substituted for the brand name of product.	

Table 3. Patent Exclusivity Period

Canada	Australia	United Kingdom
In Canada the pharmaceutical generic products are consisting patent is certain period contains 20years term from the filling application date in Canada. In these country the patent term extensions as proposed at certain meant to provide up to 5.5 years of additional exclusivity for a generic drug time period a patent protected products is on the market has been shortened by the lapse of time between the filling of a certain patent and the grating of Canada market and authorization by health Canada.	The Australia on generics products given certain patent exclusivity on date on certain submission of application as per code on (INID code 22) to obtain a full-term expiry date will be given for ascertain generic product. On the expiry of the data exclusivity period in Australia country will be adding of 5years to the certain corresponding Australian first marketing authorizing date.	On generic products in united kingdom will issuing the patent taken on a certain manner will be given 20 years on the date of submission on certain code on front page (INID code 22) to obtain get on a full- term expiry date. Initially on for extension given for a particular pharmaceutical product will be given maximum 5 years are for all pharmaceutical patents in this country.

Table 4. Legislation

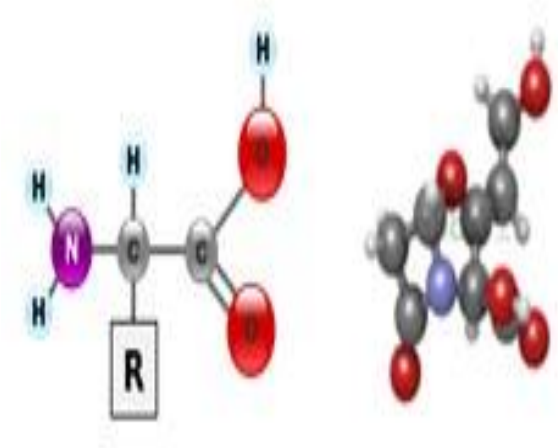
Regulations/Guidelines	Authority	Functions
Rules for the Manufacture, Use, Import, Export and Storage of Hazardous	Ministry and Government of Canada health	These rules cover the area of research as well as large scale applications of Generics products thereof and accordingly the recombinant generically products are regulated under these rules from the research and product development stage to its release into the environment.
Authority for generic drug regulation	National Association of Pharmacy Regulatory Authorities (NAPRA)	Regulation of recombinant pharmaceutical products
Guidelines for preclinical and clinical evaluation of	Department of Canadian clinical trial application(CTA)	Help in the submission of relevant data of generic product. These specifically focus on safety, purity, potency and effectiveness of the product.
Guidelines on generics.	Canadian Ministry of Health care and Family welfare (CMOHCFW) and Department of Science and technology (DMOST) (CHGTD & TPD)	(i) These guidelines ends the period of impromptu abbreviated approval pathway under which the Europe authorities had been approving Europe produced generic products with reference products approved in the Canada and Canada. (ii) These deal with the pre-market regulatory requirements including comparability exercise for quality, preclinical and clinical studies and post market regulatory requirements for generics.
Recombinant generic Safety Guidelines	Department of Occupational Health and Safety Act	These cover areas of research involving on the generic production and deliberate release of generic products, plants, animals and products.
Guidelines and Handbook for regulations of generic products.	Therapeutic Products Directorate (TPD)	Help in regulating all the generic medicine activities in compliance with other

		regulations. Provide Guidance and formats for submission of applications to Canadian government.
Health Products and Food Branch Inspectorate (HPFBI)Guidance for Industry.	Health Products and Food Branch Inspectorate (HPFBI) (Developed in conformity with D&C act and rules and GCP guidelines.)	Provides various formats to be submitted for marketing authorization of generics like: • Submission of Clinical Trial Application for Evaluating Safety and Efficacy • Requirements for permission of Drugs Approval • Post approval changes in biological products: Quality, Safety and Efficacy Documents • Preparation of the Quality Information for Drug Submission for generic Drug

Table 5. Studies Conducted In Phase I, II, III, IV Clinical Trials

Phase I –Human Pharmacology	**Phase II - Therapeutic Exploratory Trials**
Estimation of safety and tolerability with the initial administration of an investigational new drug into human(s). **Studies:** • Systemic Toxicity studies i. Single dose toxicity studies ii. Dose Ranging Studies iii. Repeat-dose systemic toxicity • Male fertility study • In-vitro genotoxicity tests • Relevant local toxicity studies • Allergenicity-Hypersensitivity tests • Photo-allergy or dermal photo-toxicity test	To determine the dose(s) and regimen for Phase III trials. **Studies:** • Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure • In-vivo genotoxicity tests • Segment II reproductive/developmental toxicity study (if female patients of child bearing age are going to be involved)
Phase III-Therapeutic Confirmatory Trials	**Phase IV- Post Marketing Trials**
To confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. **Studies:** Repeat-dose systemic toxicity Reproductive/d evelopmental toxicity studies - Segment I & III Carcinogenicity studies Carried on at least 100 patients distributed over 3-4 centers	To study the long-term effects of drugs or treatment or the impact of another factor in combination with the treatment ➢ Trials include : • Additional drug-drug interaction(s) • Dose-response or safety studies • Trials designed to support use under the approved indication(s). Ex: mortality/morbidity studies, epidemiological studies etc.

Fig 1. Chemical drugs of generic drugs



Generic structure of an alpha amino acid in un-ionized form, Generic drugs Clavulanic acid beta-lactamase blocker drug.

Fig 2. Steps involved in the Development and Marketing of generics

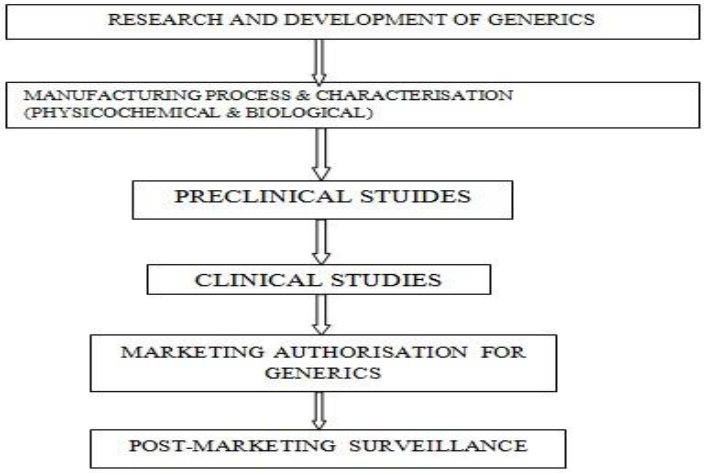


Fig 3. Registration Process of Clinical Trials in Canada

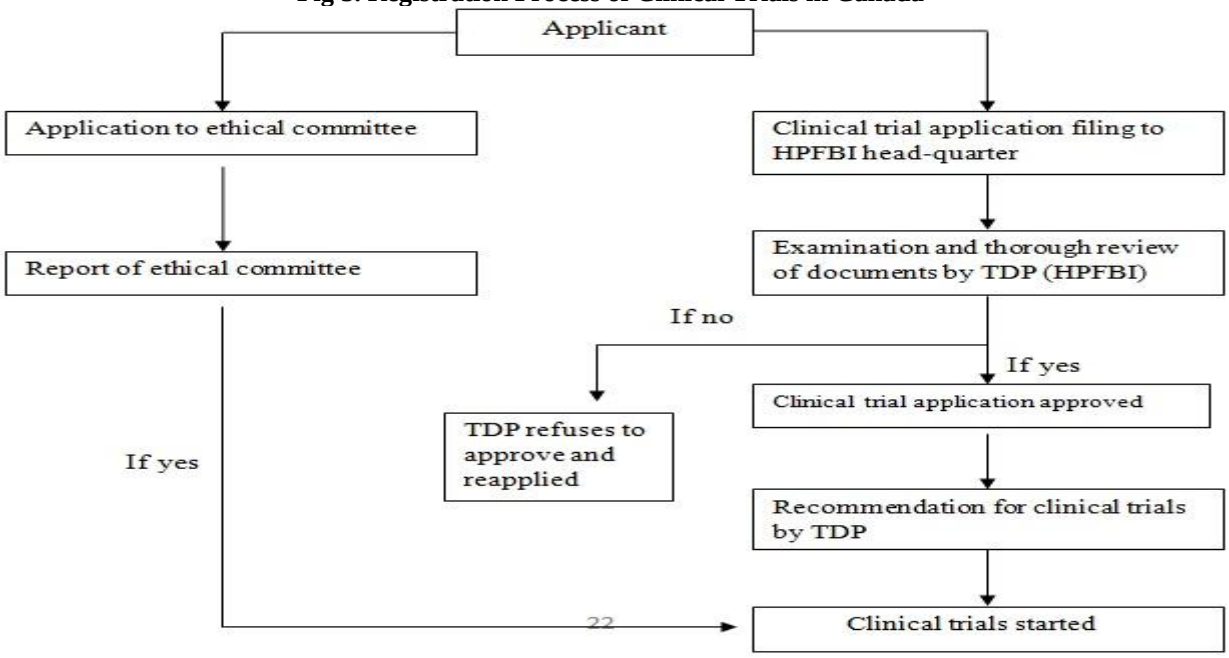
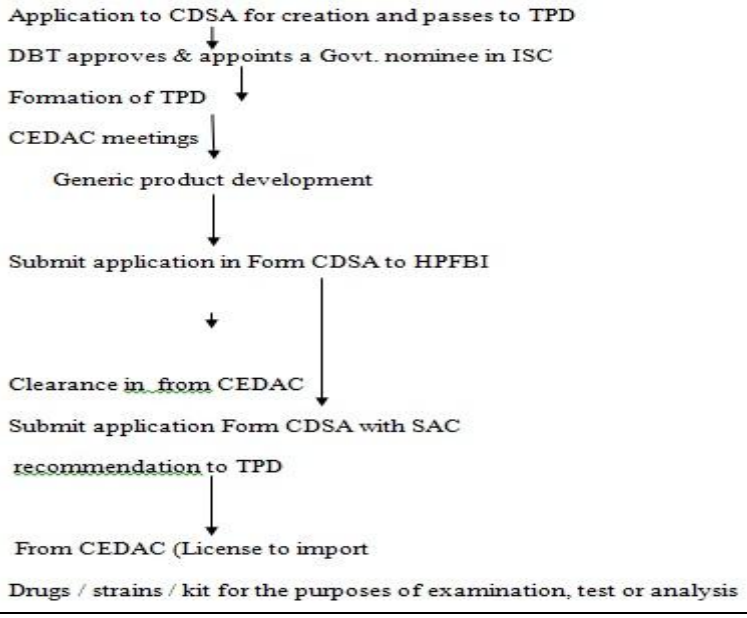


Fig 4. Stepwise procedures for the development of generics products



License for manufacture of drugs for purposes of examination, test or analysis:

Submission of application to for NOC for obtaining license is required from HPFBI of generic product is developed by pharmaceutical companies

Clinical site application to TDP

Joint inspection with HPFBI & CEDAC

NOC clearance from HPFBI

Convene TPD-Approves the 5 test batch reports

Permission for pre-clinical toxicology studies:

Submission of Application in Form C3 to

Conduct preclinical toxicology studies

Within 45 days

TPD grants permission in

conduct preclinical toxicology studies

Animal toxicity studies carried out

Depends on study duration

Animal trial data submitted Form clinical information & reports

TPD, it recommends to

HPFBI for clinical trial permission

Permission for clinical studies

Clinical site application to TDP to conduct clinical trial

Phase-1 study (Permission from TPD: 15-45 days)

Phase-1 report is submitted to HPFBI along with Phase-II protocol

Phase-II study (Permission from TPD)

Batches should be cleared by CDL, Kasauli

Phase-II report is submitted to TPD along with Phase-III protocol

Phase-III study (Permission from HPFBI)

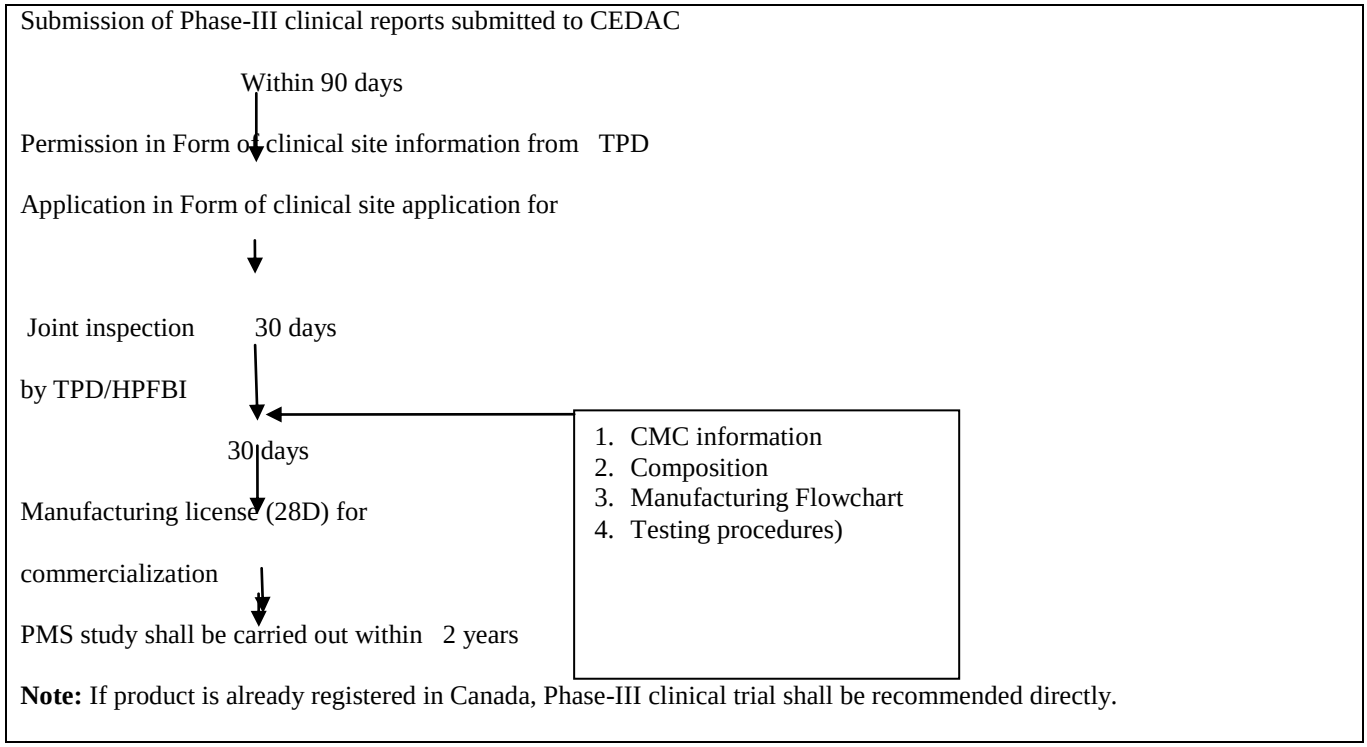
Batches should be cleared by NIB, Noida

Obtaining manufacturing permission:

Guidance for industry requirements for permission of new drug approval (HC/SC/3110, Version 1.1)

CTD format:

M1: Administrative & legal information
M2: Summaries
M3: Quality information
M4: Nonclinical information
M5: Clinical information
Two soft & hard copies to be



CONCLUSION

Canada market is in blossoming juncture of the industry life cycle with limited market and product development experience which is fast growing and has a strong economic value proposition. The development of an innovative generic is a cumbersome process for any innovator, besides stringent regulations. Hence a critical evaluation is needed for more efficient, cost effective widespread availability and marketing approval for generics. Canadian companies gain marketing capabilities, technological know-how, and regulatory process expertise from MNCs, while international companies seek to build their product pipelines and low cost manufacturing capabilities. Further, the regulations for the approval of generic products should be the responsibility of a single authorized body and should be globally acceptable. Although generics have begun to enter the global market, the generics manufacturers' long-term capability to manufacture a consistent product still remains to be proven. At present, in Canadian HPFBI Rules is in place to assess and grant marketing approval for generics. The HPFBI guidelines provide only a road map and leave challenging areas that are still to be explored and monitored; hence approvals of generic products will continue to be dealt with on a case-by-case basis. With all this, Canada is sure to be a major player as well as leader in the global generic development for the foreseeable future will compare to other countries.

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