Asia-Pacific Economic Cooperation

AHC APEC Harmonization Center

Drug Approval System of Canada

Chemical Product

December 2018

APEC Harmonization Center

Abbreviation

HC: Health Canada

HPFB: Health Products and Food Branch

TPD: Therapeutic Products Directorate

NDS: New Drug Submission

NOC: Notice of Compliance

Notice

1. Due to the purpose of this document, most of the information was quoted directly from the website or related guidelines of each economy's drug regulatory agencies.
2. When referring to the content of this document, check the up-to-date information including related laws and regulations, and revision of guidelines.

CONTENTS

Ⅰ. Drug Regulatory Agency

1. Health Canada

Health Canada (HC) is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

1.1 Organization

The organization of Health Canada is as shown in Figure 1:

As of January 4th, 2017

[Figure 1] Organization of Health Canada[1)]

1) https://www.canada.ca/en/health-canada/corporate/about-health-canada/branches-agencies.html

1.2 Task

1.2.1 Branches and Bureaus

1) Audit and Accountability Bureau
   Provides independent and objective advice and assurance on the effectiveness of risk management, controls, and governance processes

2) Chief Financial Officer Branch
   Provides strategic advice on efficiency of expenditures and value-for-money, as well as anticipating and promoting future trends

3) Communications and Public Affairs Branch
   Integrates national and regional perspectives into all of its policies and strategies, communications, and consultation functions

4) Corporate Services Branch
   Provides the administration services in the key areas of human resources management; official languages; real property and facilities management; occupational health, safety, emergency, and security management; information technology and information management

5) Departmental Secretariat
   Works with the Deputy Minister and Associate Deputy Minister of Health to support the Minster and manage departmental operations

6) First Nations and Inuit Health Branch
   Supports the delivery of public health and health promotion services on-reserve and in Inuit communities

7) Healthy Environments and Consumer Safety Branch
   Helps Canadians to maintain and improve their health by promoting healthy and safe living, working and recreational environments and by reducing the harm caused by tobacco, alcohol, controlled substances, environmental contaminants, and unsafe consumer and industrial products

8) Health Products and Food Branch

Manages the health-related risks and benefits of health products and food by:

- minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food
- providing information to Canadians, so they can make healthy, informed decisions about their health

9) Legal Services

Provides legal services, including legal policy advice, opinions, development of legislative proposals, litigation support, and assistance

10) Pest Management Regulatory Agency

Consolidates responsibilities for pest management regulation

11) Regions and Programs Bureau

Contributes to improving and maintaining the health of Canadians by effectively delivering Health Canada's regulatory, scientific, and laboratory based programs and services

12) Strategic Policy Branch

Plays a lead role in health policy, communications, and consultations

1.2.2 Agencies

1) Canadian Institutes of Health Research

Canada's major federal funding agency for health research responsible for creation of new knowledge according to internationally accepted standards of scientific excellence, and effective health services and health care system

2) Patented Medicines Prices Review Board

A quasi-judicial body that protects consumers and contributes to health care regarding the manufacturers' prices of patented medicines

3) Public Health Agency of Canada

Established to help protect the health and safety of all Canadians

1.3 Website

Health Canada: https://www.canada.ca/en/health-canada.html

Ⅱ. Related Laws and Regulations[2),3)]

1. Constitution Act

The 「Constitution Act」 imposes responsibilities on the provinces over hospitals, property, civil rights, and generally over the matters of a local nature. For example, the delivery of health care services and the health insurance plans for the general population are monitored by the provinces and territories. They regulate the practice of medicine and also play a significant role in health protection within their respective territories through various statutes including their public health legislation.

2. Canada Health Act

The criteria for the Canadian health and health insurance system are stipulated in the 「Canada Health Act」, based on the Constitution. The following five (5) criteria are known as the principles of the Act: public administration, comprehensiveness, universality, accessibility, and portability.

3. Food and Drugs Act

The 「Food and Drugs Act」 is one of the main Canadian acts that regulates the production, import, export, transport across provinces, and sale of drugs, foods, contraceptive devices, and cosmetic products. The Act is aimed at ensuring that these products are safe; their ingredients are disclosed; drugs are effective; and are not sold as foods or cosmetics. The Act consists of four (4) parts:

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2) http://laws.justice.gc.ca/

3) 「Food and Drugs Act」, consolidated version, Jun-2017

- Part I: Foods, drugs, cosmetics and devices;
- Part II: Administration and enforcement;
- Part III: Controlled drugs
- Part IV: Restricted drugs

4. Food and Drug Regulations

The 「Food and Drug Regulations」 prescribes the standards of composition, strength, potency, purity, quality or other property of food or drug. The Regulations contains the following parts:

- Part A: Administration
- Part B: Foods
- Part C: Drugs
- Part D: Vitamins, Minerals and Amino Acids
- Part E: Cyclamate Sweeteners
- Part G: Controlled Drugs
- Part J: Restricted Drugs

Ⅲ. Classification of Pharmaceutical Product

In Canada, drug products are mainly divided into "New Drugs" and "Old Drugs". In addition, there are Natural Health Products.

1. New drug[4),5)]

"New Drug" is defined as follows:

- A drug that contains or consists of a substance, whether as an active or inactive ingredient, carrier, coating, excipient, menstruum or other component, that has not been sold as a drug in Canada for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that substance for use as a drug
- A drug that is a combination of two or more drugs, with or without other ingredients, and that has not been sold in that combination or in the proportion in which those drugs are combined in that drug, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that combination and proportion for use as a drug
- A drug, with respect to which the manufacturer prescribes, recommends, proposes or claims a use as a drug, or a condition of use as a drug, including dosage, route of administration, or duration of action and that has not been sold for that use or condition of use in Canada, for sufficient time and in sufficient quantity to establish in Canada the safety and effectiveness of that use or condition of use of that drug

4) 「Food and Drug Regulations」
5) 「Food and Drugs Act」, Section C.08.001

2. Old drug

"Old Drugs" are registered for sale through a Drug Identification Number submission. Old drugs are drugs which are approved in Canada under the requirements of Division 1 of the 「Food and Drug Regulations」. Drugs under Division 1 are generally old drugs that have been on the market for a number of years, such as acetaminophen. Often these drugs are available without a prescription. When old drugs are approved for sale, the market authorization is granted through submission of a Drug Notification Form (DNF).

3. Natural Health Products[6),7),8)]

There are two (2) components for the Natural Health Products (NHP): a function component and a substance component.

The function component is related to the purpose of NHP, which is to capture those substances which are manufactured, sold, or represented for use in:

- Diagnosis, treatment, mitigation, or prevention of a disease, disorder, or abnormal physical state or its symptoms in humans
- Restoring or correcting organic functions in humans; or
- Modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

Meanwhile, the substance component is related to the fact that the NHP is derived by medicinal ingredients

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6) 「Natural Health Products Regulations」
7) Regulatory Framework: Final Report of the Advisory Panel on Natural Health Products. 1998
8) 「Guidance Document: How to Interact with the Natural Health Products Directorate Electronically」, Version 5.0, Feb-2016

4. Other categories

1) Generics[9)]

The definition is given as below:

- New drug is the pharmaceutical equivalent of the Canadian reference product
- New drug is bioequivalent with the Canadian reference product, based on the pharmaceutical and, where the Minister considers it necessary, bioavailability characteristics
- Route of administration of the new drug is the same as that of the Canadian reference product
- Conditions of use for the new drug fall within those for the Canadian reference product

2) Biologic drug[10)]

A drug listed in Schedule D[11)] to the 「Food and Drugs Act」. Biologic drugs are derived through the metabolic activity of living organisms and tend to be significantly more variable and structurally complex than chemically synthesized drugs.

3) Orphan drug[12)]

Orphan drugs are those drugs used to treat rare diseases. A rare disease is usually considered to be one that does not affect more than 650 to 1,000 people per million persons.

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9) 「Food and Drug Regulations」, Subsection C.08.002.1 (1)

10) 「Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs」, Apr-2017

11) Schedule D lists individual products (such as insulin), product classes (such as immunizing agents), references to particular sources (such as drugs, other than antibiotics, prepared from microorganisms), and methodology (such as drugs obtained by recombinant DNA procedures).

12) Policy Issues: Orphan Drug Policy, Nov-1996

Ⅳ. Drug Approval System

1. Investigational new drug application[13)]

1.1 Overview

In Canada, a Clinical Trial Application (CTA) is required before initiating clinical trials for the following categories of drugs:

- New chemical entities, prior to the issuance of a Notice of Compliance (NOC)
- Drug products marketed in Canada where the proposed trials are outside of the parameters of Notices of Compliance. These parameters include, but are not limited to: indications and clinical use, target patient populations, routes of administration, dosage regimens, and formulations.

1.2 Procedure

1) Request for a Pre-clinical Trial Application (CTA) consultation meeting
   Requests for a pre-CTA consultation meeting should be submitted in writing by the sponsor to the appropriate Directorate.
   Requests should include the following information:
   - A brief synopsis of the proposed study
   - A list of preliminary questions to be addressed by the Directorate during the meeting
   - Sufficient information for Health Canada to assess the utility of the meeting and identify the appropriate staff necessary to discuss the proposed issues

13) 「Guidance for Clinical Trial Sponsors: Clinical Trial Applications」, Mar-2016

The Directorate will acknowledge the request for consultation in a timely manner. If the Directorate agrees with the request, the acknowledgement letter will confirm the pre-CTA consultation meeting date and indicate the number of copies of the pre-CTA information package to be provided 30 days before the confirmed meeting.

2) Pre-clinical trial application (CTA) information package
The information package, which should be submitted in accordance with current electronic specifications, should contain:

- proposed agenda, any prepared slides including a finalized list of questions, and a complete list of attendees
- a brief summary of all data
- a proposed global clinical plan for the current stage of drug development including regulatory status in other countries
- details of the proposed clinical trials to be conducted in Canada, within the scope of the intended CTA
- a summary of significant Quality (Chemistry and Manufacturing) aspects of the drug, if applicable

3) Pre-clinical application consultation meeting record
The sponsor should prepare and send to the appropriate Directorate a written record of the discussions and conclusions of the consultation meeting within 14 days of the consultation date. All records of this consultation will be added to the Central Registry (CR) file for the drug. A copy of the record of discussions and conclusions approved by all parties in attendance at the meeting should be included in the subsequent CTA.

4) Clinical trial applications (CTAs)
The sponsor must file a CTA prior to the initiation of the trial. CTAs are required for human clinical trials using drugs not authorized for sale in Canada, including clinical trials in Phases I through III of drug development and comparative bioavailability studies; as well as trials involving marketed drugs, where the proposed use of the drug is outside the parameters of the Notice of Compliance (NOC) or Drug Identification Number (DIN), e.g., one or more of the following is different:

- Indication(s) and clinical use;
- Target patient populations(s);
- Route(s) of administration; or
- Dosage regimen(s).

Sponsors are not required to file a CTA for clinical trials involving marketed drugs where the investigation is to be conducted within the parameters of the approved NOC or DIN (i.e. Phase IV clinical trials).

The CTA is composed of three (3) parts (modules) in accordance with the Common Technical Document (CTD) format:

- Module 1 - Administrative and clinical information about the proposed trial
- Module 2 - Quality (Chemistry and Manufacturing) summaries about the drug product(s) to be used in the proposed trial
- Module 3 - Additional supporting quality information

5) CTA Submission

The CTA should be submitted on electronic media, accompanied by a hard copy cover letter, and be organized in accordance with the current electronic specifications.[14)]

6) CTA and CTA-Amendment Review Process

Health Canada reviews the documents submitted in CTAs and CTA-Amendments (CTA-As)[15)] to assess the quality of the products and determine that the use of the drug for the purposes of the clinical trial does not endanger the health of clinical trial subjects or other persons, the clinical trial is not contrary to the best interests of a clinical trial subject, and the objectives of the clinical trial may be achieved. All CTAs and CTA-As are subject to a 30-day default review period from the date of receipt in the Health Products and Food Branch (HPFB). An acknowledgement letter will be issued to indicate the start of the review period.

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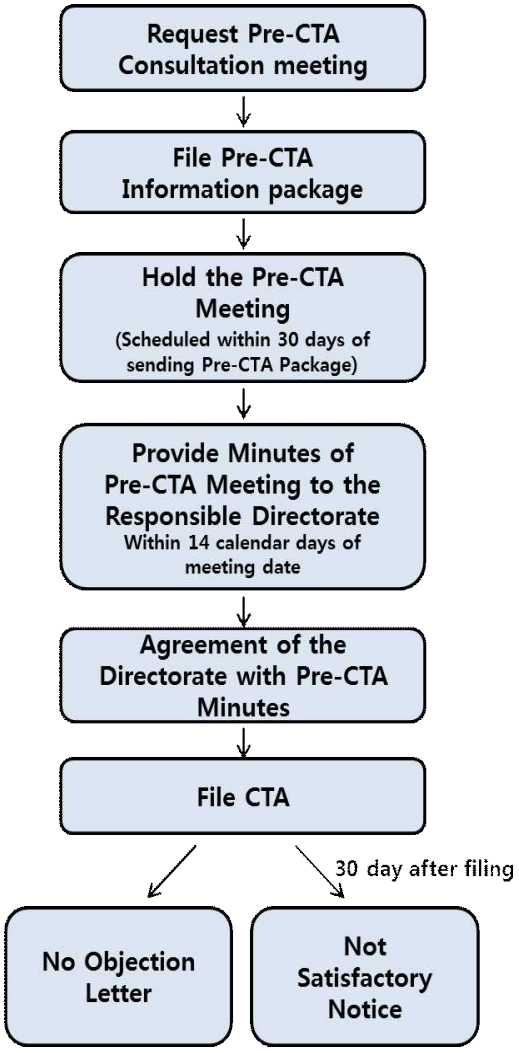
14) 「Guidance Document: Preparation of Drug Regulatory Activities in the "Non-eCTD Electronic-Only" Format」

15) CTA-As are applications in which a sponsor proposes information to support changes to a previously authorized application. CTA-As are required for changes to clinical trial drug supplies that affect the quality or safety of the drug, changes to an authorized protocol that alter the risk to clinical trial subjects, or both.

1.3 Review period



[Figure 2] Canadian CTA Submission Procedure

The clinical trial approval process is carried out by the procedure shown in the above figure, and the review of all CTAs and CTA-Amendments (CTA-As) generally takes 30-day from the date of receipt in the Health Products and Food Branch (HPFB). HPFB targets to review applications to conduct comparative bioavailability trials and Phase I trials in healthy adult volunteers within seven (7) days, with the exception of Phase I trials using somatic cell therapies, xenografts, gene therapies, prophylactic vaccines or reproductive and genetic technologies.

2. New drug application approval[16),17)]

Health Canada issues a list of drugs that they regulate as "New Drugs." Any new active substance (NAS) / new chemical entities (NCEs) require the submission of New Drug Submission (NDS). The product cannot be sold until a Notice of Compliance (NOC) will be issued for that product. The NOC is accompanied by a Drug Identification Number (DIN) number and indicates that the NDS is approved.

2.1 Overview

2.1.1 Review type[18),19)]

Drug review types in Canada are classified as follows:

- Standard reviews
- Priority reviews
- Notice of compliance with conditions (NOC/c)[20)]
- Special access programmes[21)]
- Lot release programmes
- Variations or changes to marketed drugs
- Prescription to over-the-counter (OTC) switches

16) 「Guidance for Industry: Management of Drug Submissions」, Dec-2013
17) 「Guideline: Preparation of Drug Identification Number Submissions」, Feb-1995
18) 「Guidance Document: Notice of Compliance with Conditions (NOC/c)」, Sep-2016
19) 「Guidance for Industry and Practitioners: Special Access Programme for Drugs」, Dec-2013
20) This process applies only to promising products for serious conditions that do not have all registration data currently available. When requested and granted in advance of submission, the NOC/c process is an accelerated review process
21) This applies to cases equivalent of emergency use or compassionate release.

2.1.2 Categorization of new drug application

- New Drug Submission (NDS)
- Supplement to a New Drug Submission (SNDS)
- Abbreviated New Drug Submission (ANDS)
- Supplement to an Abbreviated New Drug Submission (SANDS)
- Notifiable Change (NC)
- Applications for Drug Identification Number(DINA)

2.1.3 Drug identification number[22)]

A Drug Identification Number (DIN) is an eight-digit numerical code assigned to each drug product marketed under the 「Food and Drugs Act」 and 「Regulations」. Once a drug has been authorized, Health Canada issues a DIN which permits the manufacturer to market the drug in Canada. For drugs that are New Drugs (after 1965), there is a more stringent review (an NDS must be submitted) and the drug is required to have an NOC in order to be marketed in Canada.

A DIN contains the following product information:

- manufacturer
- brand name
- medicinal ingredient (s)
- strength of medicinal ingredient (s)
- pharmaceutical form
- route of administration

22) 「Guideline: Preparation of Drug Identification Number Submissions」, Feb-1995

2.2 Procedure[23)]

The following process describes review process for a new drug in Canada:

1) A sponsor who wishes to market a drug in Canada shall submit a "New Drug Submission" to HPFB. This contains information and data about the drug's safety, effectiveness and quality. It also includes the results of the preclinical and clinical studies, whether done in Canada or elsewhere, details regarding the production of the drug, packaging and labelling details, and information regarding therapeutic claims and side effects.

2) HPFB performs the following in sequential order:
   - Thorough review of the submitted information, sometimes using external consultants and advisory committees
   - Evaluation of the safety, efficacy, and quality data to assess the potential benefits and risks of the drug
   - Review of the information provided to healthcare practitioners and consumers about the drug (e.g. the label, product brochure).

3) If, at the completion of the review, the conclusion is that the benefits outweigh the risks; and that the risks can be mitigated, the drug is issued a Notice of Compliance (NOC), as well as a Drug Identification Number (DIN) which permits the sponsor to market the drug in Canada and indicates the drug's official approval in Canada.

   In addition, Health Canada laboratories may test certain biological products before and after authorization to sell in Canada has been issued. This is done through its Lot Release Process, in order to monitor safety, efficacy, and quality. TPD/BGTD uses external consultants/experts on an ad hoc basis.

23) https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fact-sheets/drugs-reviewed-canada.html

2.3 Required dossiers[24),25)]

The Common Technical Document (CTD) is a basis for the standard format of a marketing authorization application. Drugs in Canada are classified into “Old Drugs” and “New Drugs”. For New Drugs, a New Drug Submission (NDS) for marketing authorization is required; while for Old Drugs, a Drug Identification Number (DIN) Submission is required. It is expected that all submissions filed as provided in the 「Food and Drug Regulations」, will follow the CTD format. Health Canada is trending towards accepting regulatory submissions in the e-CTD format only and is considering not accepting the paper format in the near future. In case of Supplements and Notifiable Changes (NCs), applicants would provide only the relevant modules affected by the change. For CTD modules in NDS, refer to Appendix 1.

2.3.1 Stability test

Canada falls under climate zone I. Stability tests should be conducted under at minimum of three (3) primary batches. Two (2) of the three (3) batches should be at least pilot scale batches and the other batch may be smaller than others.

Test	Conditions	Minimum test period required for data submission
Long term (real time) test	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months (0, 3, 6, 9, 12, 18, 24, 36 months, etc.)
Accelerated test	40°C ± 2°C/75% RH ± 5% RH	6 months (0, 3, 6 months)
Intermediate test	30°C ± 2°C/65% RH ± 5% RH	6 months (0, 6, 9, 12 months)

[Table 1] Stability Test Conditions

24) 「Guidance Document: Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format」, May-2012.

25) 「Guidance Document: Preparation of Drug Regulatory Activities in the “Non-eCTD Electronic-Only” Format」, Oct-2016

2.4 Regulatory consultation system[26)]

Like pre-CTA meeting, sponsors may request for pre-new drug submission (pre-NDS) meeting. The purpose of the meeting is to discuss the presentation of data in support of the submission. Meeting requests are to be submitted to the appropriate Regulatory Affairs Division in the Biologics and Genetic Therapies Directorate (BGTD) or Regulatory Project Manager in the Therapeutic Products Directorate (TPD) in writing or by fax no less than 1 month prior to the proposed meeting date; and should include the following information:

- Purpose of the meeting
- A brief description of the product
- Three (3) proposed dates for the meeting, including whether an afternoon or morning meeting is being requested

26) 「Guidance for Industry: Management of Drug Submissions」, Dec-2013

2.5 Review period[27)]

For standard New Drug Submissions (not under an expedited timeline such as priority review) it generally takes approximately 12 to 14 months for TPD/BGTD to reach a decision. New Drug Submissions that have been granted priority review status take approximately eight (8) months for making a decision.

Type	Screening	Review	Screening response to NON	Review of response to NON	Review of response to NOC/c-QN
1. Priority - NAS, Clinical or Non-Clinical /C&M, Clinical or Non-Clinical Only	25	180	25	90	30
2. NOC/c - NAS, Clinical or Non-Clinical /C&M, Clinical or Non-Clinical Only	25	200	25	90	30
3. NAS	45	300	45	150	30
4. Clinical or Non-Clinical Data/C&M	45	300	45	150	30
5. Clinical or Non-Clinical Only	45	300	45	150	30
6. C&M/Labelling	45	180	45	150	0
7. Published Data	45	300	45	150	0
8. Labelling Only	7	60	0	0	0
9. Administrative data(product or manufacturer name changes)	45	0	0	0	0

C&M: Chemistry & Manufacturing/Quality

NAS: New Active Substance

NON: Notice of Non-compliance

NOC/c: Notice of Compliance with Conditions

[Table 2] Target Review Period of New Drug Submission

27) 「Guidance for Industry: Management of Drug Submissions」, Dec-2013.

3. Generic drug approval application

Generic products are approved through Abbreviated New Drug Submissions (ANDSs). Generally, all second-entry or subsequent market entry products, as well as reformulated products belonging to the originator, qualify for ANDS format.[28)]

3.1 Reference medicinal product (RMP)[29)]

The Reference Medicinal Product (RMP) is referred to in Canada as the "Canadian Reference Product" (CRP) which means:

- a drug in respect of which a notice of compliance is issued and which is marketed in Canada by the innovator of the drug
- a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics, where a drug in respect of which a notice of compliance has been issued cannot be used for that purpose because it is no longer marketed in Canada
- a drug, acceptable to the Minister, that can be used for the purpose of demonstrating bioequivalence on the basis of pharmaceutical and, where applicable, bioavailability characteristics

The acceptance criteria for the use of a non-Canadian reference product are outlined in the TPD Policy on Canadian Reference Product. In Canada, there is a great difficulty in filing an ANDS without using a Canadian Reference Product. Unfortunately, there is no Reference Medicinal Product Listing in Canada, but Canadian Reference Product is searchable from the NOC Database available on the TPD website.[30)]

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28) 「Food and Drug Regulations」, Subsection C.08.002.1 (1)
29) 「Food and Drug Regulations」, Subsection C.08.001.1
30) http://webprod5.hc-sc.gc.ca/noc-ac/index-eng.jsp

3.2 Procedure[31)]

ANDS procedure requires an attestation checklist to assist sponsors in ensuring that the submission filed is complete and that key necessary information supporting the submission is provided in the filing. Generic manufacturers are expected to include a completed attestation form in their submission in order to specify that this required information has been provided.

Sponsors are asked to contain the completed attestation form in both PDF and Word format in their ANDS. Failure to submit a completed attestation form will lead to an issuance of a Screening Deficiency Notice. However, the checklist is not required for either submission of a supplemental ANDS or Labelling-Only submission.

3.3 Required dossier[32)]

In general, for solid oral dosage forms, a bioequivalence study is required to be performed versus the Canadian Reference Product. A copy of the study data and complete Chemistry and Manufacturing data filed in the Common Technical Document format are required for an ANDS. When using the CTD format for an ANDS, the submission should be organized similarly to an NDS, although only certain sections or modules may be necessary depending on the submission and/or changes. The applicants for ANDS would normally submit the following data:

- Module 1: Administrative and Product Information (For Canada)
- Module 2.1: CTD Table of Contents
- Module 2.2: Introduction
- Module 2.3: Quality Overall Summary
- Module 3: Quality data
- Module 5.1: Table of Contents for Module 5

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31) Notice: Updated Screening Criteria for Generic Drug Submissions, Jan-2013

32) 「Draft Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format」, May-2004

- Module 5.2: Tabular Listing of all Clinical Studies
- Module 5.3.1.2: Comparative Bioavailability and Bioequivalence Study Reports
- Module 5.3.1.4: Reports of Bioanalytical and Analytical Methods for Human Studies
- Module 5.4: Literature References

As of June 1, 2016, Health Canada no longer accepts required dossiers submitted in writing. If a company is not ready to file in the eCTD format, it may file required documents in the "non-eCTD electronic-only" format as an interim option until transition to the eCTD format has been completed.

3.4 Patent-approval linkage system

The 「Patented Medicines (Notice of Compliance) Regulations」 specifies the link between Notice of Compliance and patent in Canada, including: 1) drawing up a patent list associated with approved medicines and 2), and automatic stay that suspends the generic drug approval process if the patent holder files a lawsuit based on the registered patent.

According to the Canadian automatic stay system, once the patent holder files a lawsuit within 45 days from the date of notice, approval will be suspended automatically during a 24-month period. However, the competent court may dismiss the lawsuit at an early stage in case of exercising the rights improperly such as a claim for approval prohibition based on registered patent lacking relation with new drug. Also, if such a claim by the patent holder for the prohibition is withdrawn or suspended, or dismissed, it is possible for a generic drug company to put in a claim for damages.

4. Orphan drugs[33)]

In Canada, there is no specific orphan drug policy, but there is a concern for promoting the development of orphan drug in Canada by means of tax incentives and special market protection. Orphan drugs usually are subject to priority review in Canada, given 180 days of a time for target drug submission review. Orphan drugs may also be subject to Notices of Compliance with Conditions (NOC/c). For cost recovery (i.e. a fee for the review of all new drug submissions, including orphan drugs), there is an option to file for fee remission if the fee for review of the application is greater than 10% of the anticipated gross revenue for sales over a three year period.

On October 3, 2012, the Minister of Health announced two (2) initiatives for Canadians with rare diseases: 1) A new regulatory framework will be established by the Government, which is specifically designed for review and approval of orphan drugs used to treat small populations of patients, in addition to 2) the launch of Orphanet Canada website. The information about rare diseases is now available on the Orphanet Canada web portal.[34)]

33) Policy Issues: Orphan Drug Policy, Nov-1996
34) http://www.orpha.net/consor/cgi-bin/index.php?lng=EN

5. Priority review[35)]

Priority review is intended to enable faster access to new therapies, preventatives, and diagnostic agents for serious, life-threatening or severely debilitating diseases or conditions. A New Drug Submission (NDS) or Supplemental New Drug Submission (SNDS) will be granted the priority review status for a serious, life-threatening or severely debilitating illness, for which there is substantial evidence of clinical effectiveness that the drug provides:

- Effective treatment, prevention or diagnosis of a disease or a condition for which no drug is currently marketed in Canada; or
- A significant increase in efficacy and/or a significant decrease in risk, such that the overall benefit/risk profile is improved over existing therapies, preventatives, or diagnostic agents for a disease or a condition that is not adequately controlled by a drug marketed in Canada.

In defining whether "a condition is serious", Health Canada believes that a matter of discretionary judgment is required. Factors such as survival, day-to-day functioning or the likelihood that the disease if left untreated, will progress from a less severe condition to a more serious one are all taken into account. The latter includes, but is not limited to:

- Acquired immunodeficiency syndrome (AIDS)
- All other stages of human immunodeficiency virus (HIV) infection
- Alzheimer's dementia
- Amyotrophic lateral sclerosis (ALS)
- Angina pectoris
- Heart failure
- Cancer
- Other diseases those are clearly serious in their full manifestations

35) 「Guidance for Industry: Priority Review of Drug Submissions」, Nov-2005

5.1 Review Period

Submissions granted with priority review status will be subject to the following reduced target timeframes:

- 10 calendar days: processing within the Submission Management Division of the appropriate Directorate
- 25 calendar days: submission screening
- 180 calendar days: submission review

6. Renewal

There is no procedure for renewal of approvals in Canada. However, there is a requirement for all Drug Identification Number (DIN) owners to confirm annually (for all approved products, before October) that the information previously supplied with regard to each product is correct through a process called the Annual Drug Notification. This requirement applies to ALL products that have a DIN assigned to them, not just those that are marketed. Failure to submit the Annual Drug Notification Form for all products may result in the cancellation of existing DINs. Since 2012 Health Canada receives the Annual Drug Notifications electronically.[36)]

36) Notice: Annual Drug Notification Package is Now being Sent Electronically, Jul-2012

7. Pharmacovigilance and risk management

7.1 Pharmacovigilance[37),38)]

The 「Food and Drugs Act」 includes the provisions covering the pharmacovigilance of drug products. Division 5 of the 「Food and Drug Regulations」 covers the pharmacovigilance responsibilities regarding clinical trials while Division 1 covers the post-marketing pharmacovigilance responsibilities to drugs.

The Canada Vigilance Program is part of the MedEffect Canada Initiative, which was created in 2005 to improve access to new safety information and adverse reaction reporting as well as to provide a single window approach to post-market surveillance activities and programs related to health products marketed in Canada.

The Canada Vigilance Program collects and assesses reports of suspected adverse reactions to marketed health products in Canada, including prescription and non-prescription medications; natural health products; biologically derived products such as vaccines and fractionated blood products; cells, tissues and organs; radiopharmaceuticals; and disinfectants and sanitizers with disinfectant claims. Adverse reaction reports are submitted voluntarily to Health Canada by Canadian health professionals and consumers. Market Authorization Holders (manufacturers and distributors) and source establishments are required to report adverse reactions as mandated by the 「Food and Drugs Regulations」, 「Natural Health Product Regulations」 and 「Safety of Human Cells, Tissues and Organs for Transplantation Regulations」. This information is one of the tools that enable Health Canada to monitor the safety profile of health products to determine if their benefits continue to outweigh their risks.

Health Canada has collected reports of suspected adverse reactions since 1965 and currently receives daily adverse reaction reports, including new reports and additional information for reports previously submitted.

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37) 「Guideline: Health Product Vigilance Framework」, Sep-2012

38) Canada Vigilance - A New Name for the Canadian Adverse Drug Reaction Monitoring Program, Oct-2007

Seven (7) regional offices (called Canada Vigilance Regional Offices) support the Canada Vigilance Program, providing local points of contact for health professionals and consumers. Adverse reaction reports are collected regionally and forwarded to the National Office for further analysis. Market Authorization Holders send reports directly to the National Office.

Also, there are some country-specific pharmacovigilance requirements. For "new drugs" marketed in Canada, domestic reports of unusual failure in efficacy must be reported to the Marketed Health Products Directorate (MHPD) within 15 calendar days of the receipt of information by the Market Authorization Holder (MAH).

The underlying principle is that if a health product fails to produce the expected intended effect, there may be an adverse outcome for the patient, including an exacerbation of the condition for which the health product is being used. Clinical judgment should be exercised by a qualified health care professional from the MAH to determine if the problem reported is related to the product itself, rather than one of treatment selection or disease progression since health products cannot be expected to be effective in 100% of the patients.

7.2 Risk management plan[39)]

Health Canada has adopted and integrated the use of Risk Management Plans (RMPs) and ICH Guideline into the regulatory review of drugs in Canada. RMPs are submitted to Health Canada either as part of a submission [e.g., New Drug Submission (NDS) or Supplemental New Drug Submission (S/NDS)].

RMPs are requested for:

- New pharmaceutical submissions that include a new active substances (NAS)
- All biologics and subsequent entry biologics (which include biotechnology products, vaccines, and fractionated blood products)
- All radiopharmaceutical drugs

39) 「Guidance Document: Submission of Risk Management Plans and Follow-up Commitments」, Jun-2015

- Any drugs to be marketed that were previously withdrawn due to serious safety issues
- Drugs with a significant change in indication
- Drugs with the designation "Extraordinary Use"

RMPs not linked to a NDS or S/NDS can be requested for, but not limited to:

- A marketed drug for which a serious safety issue has been identified
- A previously acceptable RMP which has undergone significant changes
- Drugs new to a class for which a serious or potentially serious safety risk has been identified to another member of the class.

RMPs (or sections of the RMP) may be requested for generic drugs; and also by Health Canada as part of an ongoing review or other situations in order to support informed regulatory decision making about the drug. Health Canada generally accepts the RMP in EU format, but other recognized formats; provided that they include all the essential elements of the EU RMP (i.e., safety specification, pharmacovigilance activities, risk minimization activities, and evaluating effectiveness of risk minimization measures) as well as any additional information specific to the Canadian context are also acceptable.

Ⅴ. Others

1. Good Manufacturing Practice[40),41),42)]

Good Manufacturing Practice (GMP) inspectors are regionally located in Canada and inspect Canadian facilities on regular basis. The inspectorate monitors this through Site Reference Files, internal audit data, and foreign government inspection reports.

Canada has made Mutual Recognition Agreements (MRAs) with the European Union, Switzerland, the European Economic Area – European Free Trade Association, and Australia. MRAs are under discussion with the US. MRAs mean that inspections from other foreign countries could be more easily recognized in Canada. GMP in Canada is firmly linked to validation.

1.1 GMP Inspection[43)]

When compliance with GMP is evaluated, risks will be assessed through observed deviation. Factors to be considered include the degree and nature of the deviation in relation to the product concerned. Manufacturing, packaging/labelling, importing, distribution, wholesales, and testing labs are required to have establishment licenses. Only facilities in Canada may have an establishment license. The importer is responsible for ensuring that the foreign facility complies with Canadian GMP. Inspections of all facilities with an establishment license are carried out by the inspectorate. The inspection cycles include every 24 months for fabricators, packager/labelers, and testing labs, and every 36 months for importers, distributors, and wholesalers.

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40) Notice: Annual Drug Notification Package is Now being Sent Electronically, Jul-2012
41) Questions and Answers: Yearly Biologic Product Reports (YPBR), Mar-2008
42) 「Guideline: Good Manufacturing Practices (GMP) Guidelines for Active Pharmaceutical Ingredients (APIs)」, Dec-2013
43) 「Guideline: Risk Classification of Good Manufacturing Practices (GMP) Observations」, Sep-2012

1.2 GMP assessment of oversea manufacturing product[44)]

The following information will be accepted as evidence of GMP compliance for foreign sites. Where the original information is available in a language other than English or French, the copy of the original information must be provided with an attestation on the accuracy of the translation by the translator.

1) For sites located in a MRA country
   - Name of each fabricator, packager/labeler, and tester of the drug
   - Address of each building at which the drug is fabricated, packaged/labelled, or tested
   - Activities of building and drug category
   - Name of the regulatory authority in the MRA country

   Once an MRA foreign site is listed on a drug establishment license (DEL), Health Canada no longer asks DEL holders to submit an application to renew the GMP evidence of an MRA foreign building.

2) For sites not located in a MRA country or for sites located in a MRA country for products or activities not covered under the MRA
   - A certificate from a Canadian inspector indicating that the fabricator/ packager/labeller's or tester's buildings, equipment, practices, and procedures meet the applicable requirements.
   - Activities of building and drug category

44) 「Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites」, Aug-2009

2. Drug Master File[45)]

A Drug Master File (DMF) or Master File (MF) is a reference that provides information about specific processes or components used in manufacturing, processing, and packaging of a drug. Filing of a DMF is optional in Canada, but the DMF is a useful vehicle for providing information to Health Canada (HC) since such information is of a proprietary nature and is not available to the manufacturer of dosage form.

Health Canada does not have a database that is accessible to the public listing of all DMFs registered in Canada. A DMF is reviewed only in connection with a specific drug submission wherein a Letter of Access (LOA) has been provided by the DMF owner or agent allowing the sponsor of the drug submission to cross-reference confidential information. It is recommended that DMFs are filed no more than a year, but no less than two (2) months prior to the filing of a drug submission or clinical trial application making reference to those DMFs.

3. Labelling and package inserts[46),47)]

Labelling of prescription drugs in Canada may be in either English or French with the following two (2) exceptions:[48)]

- Labelling for clinical trial supplies is required to be in both English and French.
- If a non-prescription product is available for self-selection, then adequate directions for use must be in both English and French.

3.1 General information

1) Inner and outer labels[49)]

The inner and outer labels shall contain the following:

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45) 「Draft Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements」, Feb-2016
46) 「Guidance Document: Labelling of Pharmaceutical Drugs for Human Use」, Jun-2015
47) Regulations: Amending the Food and Drug Regulations (Labelling, Packaging and Brand Names of Drugs for Human Use) - SOR/2014-158, Gazette II, Jun-2014
48) 「Food and Drug Regulations」, Section A.01.015, Jul-2017
49) 「Food and Drug Regulations」, Section C.01, Jul-2017

- On the principal display panel
  - The drug name, if any of the drug which, if there is a brand name for the drug, shall immediately precede or follow the brand name in type not less than one-half the size of that of the brand name. If there is no proper name, the common name of the drug may be used.
  - If the drug is a Canadian Standard Drug, a statement that it is a Canadian Standard Drug, for which the abbreviation C.S.D. may be used.
  - In case of the sterile drug, the notation "sterile" and "stérile" shall be used.
  - The Drug Identification Number assigned by Health Canada for the drug, preceded by the words "Drug Identification Number" or the letters "DIN".

- On the upper left quarter of the principal display panel
  - The following symbol if the drug is required to be sold on prescription

    Pr

  - The following symbol in a clear manner and a conspicuous color and size, in case of controlled drugs

    

  - The following symbol in a color contrasting with the rest of the label or in type not less than half the size of any letters used thereon, in case of narcotics

    

  - In case of targeted substances, T/C in a color contrasting with the rest of the label and in type not less than half the size of any other letter used on the main panel

    T/C

- On any panel
  - Name and address of the manufacturer
  - Lot number
  - Adequate directions for use
  - A quantitative list of the medicinal ingredients of the drug by their proper names or, if they have no proper names, by their common names
  - Expiration date
  - The name and address of the principal place of business in Canada of the person responsible for the sale of the drug
  - Phone number, email address, website address, postal address, or any other information that enables communication with a contact person in Canada in both English and French
  - A statement to the effect that any injury to a person's health that is suspected of being associated with the use of the drug maybe reported to the company contact person

2) Outer label

Outer labels shall show the following:

- Net amount of the drug in the container in terms of weight, measure, or number
- In the case of a drug intended for parenteral use, a quantitative list of any preservatives present therein by their proper names, or if they have no proper names, by their common names
- In the case of a drug for human use that contains mercury or a salt or derivative thereof as a preservative, a quantitative list of all mercurial preservatives present therein by their proper names, or if they have no proper names, by their common names.

3) Small containers

For containers that are too small to accommodate an inner label that conforms to the requirements of the Regulations, the inner label requirements do not apply if there is an outer label that complies with the labelling requirements of the Regulations.

4) Adequate directions for use

Adequate directions for use generally cover the indication for which the drug is to be used and the dosage, as well as any contra-indications, precautions, warnings, or adverse reactions that are necessary for the use of the drug. Storage conditions are also included. Frequently, adequate directions for use cannot fit on a container or label. In those instances, a package insert can accompany the drug.

5) Font size requirement and readability[50),51)]

There is no font size requirement in Canada written into the 「Food and Drug Regulations」, with the exception of the narcotic symbol and the need for the Proper Name to be in letters half the size of the brand name. The size of font is judged by the small letter "o". The 「Food and Drug Regulations」 requires that the content of every drug label be:

- prominently displayed
- readily discernable to the consumer under normal conditions of purchase and use
- be expressed in "plain language".

Health Canada recommends a minimum font size of nine (9) points for inner and outer labels, including any text in a table format. All labelling should be in *Sans Serif* type font. A point size of no less than six (6) should be used for inner labels for small and special containers.

50) 「Food and Drug Regulations」, Section A.01.017

51) 「Guidance for Industry: Good Label and Package Practices Guide for Prescription Drugs」, Jun-2016

3.2 Package insert/leaflet[52)]

There are two (2) kinds of package insert in Canada: professional insert and patient insert. Most products in Canada are not accompanied with professional package insert, but they are becoming more common. The label of a product usually states that the Product Monograph is available on request when the professional package insert is not included. Professional package inserts are common for parenteral products.

For drugs that are old drugs, companies generally develop documents that are similar to Product Monographs, and call them prescribing information. They then proceed to develop either professional or patient inserts based on the prescribing information that they have developed.

For drugs that have patient package inserts, they are expected to be provided to the patient at the point of dispensing or sale. If there is no patient package insert, it is Health Canada's expectation that the company supplies the information to the pharmacist (or doctor), who will distribute the information to the patient.

Health Canada recommends a font size of ten (10) points for the consumer information/patient medication information and package insert text and a minimum of nine (9) points for inner and outer labels and tables for the labelling of the consumer information/patient medication information and package inserts, preferably all labelling in *Sans Serif* type font, to avoid any problems in legibility.

52) 「Guidance Document: Product Monograph」, Dec-2016

3.3 Summary of product characteristic information for healthcare professionals[53),54),55)]

Product Monographs are required to be submitted in either English or French; and available in both languages at the time of sale. A Product Monograph shall not be submitted in another language other than English or French since the document is specifically developed for Canada.

1) Title page

The title page should bear the following information in the following sequence:

- The words "Product Monograph"
- Symbol (e.g., Pr, N, T/C), as applicable
- Brand name of the drug
- Proper name or common name of the drug substance(s)
- Strength(s) and dosage form(s)
- Pharmaceutical standard (e.g., prescribed, pharmacopoeial or professed), as applicable
- Therapeutic, diagnostic or pharmacological classification and code in accordance with the World Health Organization's Anatomical Therapeutic Chemical (ATC) index
- Name, place of business and website of the sponsor, and, when appropriate, the name and place of business of the distributor
- Date of the initial preparation or the most current revision
- Submission control number (if available)

2) Table of contents

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53) Regulations: Amending the Food and Drug Regulations (Labelling, Packaging and Brand Names of Drugs for Human Use) - SOR/2014-158, Gazette II, Jun-2014

54) Frequently Asked Questions: Product Monographs Posted to the Health Canada Website, Jul-2014

55) Notice: Final Release - Part I: Health Professional Information and Part II: Scientific Information of the Guidance Document: Product Monograph, Dec-2016

3) Health professional information

Summary product information

- Indications and clinical use
- Contraindications
- Warnings and precautions
- Adverse reactions
- Drug interactions
- Dosing and administration
- Overdosage
- Action and clinical pharmacology
- Storage and stability
- Special handling instructions
- Dosage forms, composition and packaging

4) Scientific information

Pharmaceutical information

- Clinical trials
- Detailed pharmacology
- Microbiology
- Toxicology
- References

5) Patient medication information

The patient medication information section is a plain language translation of information contained in Parts I and II of the product monograph. Plain language means using the simplest, most common words as possible, so that information is clear, concise and easy to understand for the intended audience.

4. Certificate of Pharmaceutical Product[56)]

Frequently, countries ask for certification of the GMP status of the manufacture of the drug product from Canada. In these instances, companies use a Certificate of Pharmaceutical Product (CPP). It is the format recommended by the WHO, which establishes the marketing status of the product in the country of origin and the GMP status of the applicant. When the pharmaceutical product is fabricated and packaged/labeled in Canada, a CPP is issued if all the following requirements are met:

- Fabricator and packager/labeler are GMP compliant.
- The pharmaceutical product has a valid DIN and a valid date of notification.
- The pharmaceutical product is sold on the Canadian market.
- The applicant must be located in Canada.

When the pharmaceutical product is fabricated in a foreign country and packaged/labeled in Canada; or fabricated in Canada and packaged/labeled in a foreign country, a CPP is issued if all the following requirements are met:

- Packager/labeler and the fabricator are GMP compliant.
- The foreign establishment is GMP compliant and is listed on the Canadian Drug Establishment Licence (DEL).
- The pharmaceutical product has a valid DIN or an NOC and a valid date of notification.
- The pharmaceutical product is listed on the Canadian market.

When the pharmaceutical product is fabricated and/or packaged/labeled in Canada, but not marketed in Canada; a CPP is issued if the following conditions are met:

- The fabricator and/or packager/labeler are/is GMP compliant.
- A DIN or an NOC has been issued.

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56) Questions and Answers: Importation and Exportation, Jan-2008

5. Import and export

5.1 Import[57),58)]

All drugs commercially imported into Canada must meet all applicable requirements of the 「Food and Drugs Act」 and its associated 「Regulations」, including, but not limited to, labeling and marketing authorization requirements, Establishment Licensing or Site Licensing requirements (including foreign sites as regulated), and Good Manufacturing Practices (GMP) requirements. Importation of drugs which are not compliant at the time of import are subject to an Advance Notice of Importation – prior to each importation.

Type of Drug	Import Requirements
Prescription drugs	• A DIN for each product • Importer must hold an Establishment License (EL) and also must be a practitioner, a drug manufacturer, a wholesale druggist or a registered pharmacist • The foreign manufacturing site must be listed on the importer's EL. • API supplier(s) information must be amended to Importer's Table A.[59)]
Over-the-counter drugs (OTC)	• A DIN for each product • Importer must hold an EL • The foreign manufacturing site must be listed on the Importer's EL. • API supplier(s) information must be amended to Importer's Table A.
Products imported under the Special Access Program (SAP)	• A Letter of Authorization (LOA) issued by the SAP of Health Canada authorizing the sale/use of a pharmaceutical product for each instance • A copy of this authorization must be provided at the port of entry.
Products imported for use in a clinical trial (Other than phase IV)	• A No Objection Letter (NOL) issued by the Therapeutic Products Directorate (TPD) or the Biologics and Genetic Therapies Directorate (BGTD) of Health Canada authorizing the use of the drug in a clinical trial • A copy of this authorization must be provided at the port of entry.

[Table 3] Importation Requirements

57) 「Guidance Document on the Import Requirements for Health Products under the Food and Drugs Act and its Regulations」, Jun-2010

58) Policy: Health Products and Food Branch Inspectorate Import and Export Policy for Health Products Under the Food and Drugs Act and its Regulations, Jun-2010

59) Table A is part of the Drug Establishment Licence (DEL) Application Form (FRM-0033) and must be completed for all Foreign Buildings that fabricate, package/label and test active pharmaceutical ingredients.

5.2 Export[60)]

Health products exported from Canada must meet the relevant requirements of the 「Food and Drugs Act」 and its Regulations.

A health product may be exported from Canada that has been fabricated by a Canadian licence holder (Establishment, site, etc.) to a Canadian market authorized formulation/design (Drug Identification number (DIN), etc.). If the health product is fabricated in Canada for the sole purpose of export and is therefore not sold for consumption in Canada, the product is not required to be labeled with the Canadian approved product labeling. However, the labelling should indicate the product is for export only. The manufacturer should also attest that the product is not known to contravene any laws of the importing country. If requested Health Canada may issue for these products a certificate (Certificate of Pharmaceutical Products (CPP), Manufacturer's Certificates, etc.).

A health product fabricated for use in a clinical trial involving human subjects may be exported if it meets the applicable requirements of the 「Food and Drugs Act」 and its 「Regulations」 for a clinical trial conducted in Canada.

60) Policy: Health Products and Food Branch Inspectorate Import and Export Policy for Health Products Under the Food and Drugs Act and its Regulations, Jun-2010

6. Manufacturing licence[61),62)]

6.1 Overview

A Drug Establishment Licence (DEL) is required for any person in Canada engaged in any of the six (6) licensable activities, which are as follows: fabricate, package/label, test, import, distribute, and wholesale. A DEL is also required for active pharmaceutical ingredients (API) to engage in the first four activities. The DEL is issued by the Health Products and Food Branch Inspectorate (HPFBI).

6.2 Application for a Drug Establishment License

All new DEL applicants will have their facility GMP inspected by a Regions and Programs Bureau (RAPB) inspector to determine if appropriate processes are in place to conduct the required licensable activities. HPFBI expects that applications will only be submitted once the establishment is ready for an inspection and to begin licensable activities.

In order for a foreign site to conduct the licensable activities of fabricate, package/label or test on behalf of a Canadian Establishment, the foreign site must first be assessed for drug GMP compliance, or API GMP compliance for foreign API test sites, by HPFBI. The information for assessment must be submitted as part of the DEL application and must meet the requirements of 「Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites」. The Guidance details the evidence required in support of GMP compliance for two (2) categories of sites:

- Foreign sites that have signed a Mutual Recognition Agreement (MRA) with Canada[63)]
- Foreign sites in non-MRA countries

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61) 「Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites」, Aug-2009
62) 「Guidance Document: Drug Establishment Licences and Drug Establishment Licensing Fees」, Apr-2013
63) For a current list of MRA countries, refer to Regulatory Intelligence Report: International Agreements & Cooperation.

Licensable activities may only occur at a foreign site on behalf of a Canadian establishment if sufficient evidence in support of foreign site GMP compliance was provided and deemed acceptable by HPFBI. A site deemed compliant will be added to the foreign site annex of the Canadian Drug Establishment Licence (DEL).

Importers of drugs and APIs must complete Table A for the DEL application; this includes information for foreign API manufacturing, packaging/labelling and testing sites. Importers of drugs and APIs must maintain valid inspection reports for the foreign API sites.

7. Fees[64),65)]

All payments must be made in Canadian currency. Human drug (pharmaceutical and biological) submission and application review fees are as shown in Table 4.

Unit: CAD (As of April 1, 2018)

Fee Category	Description	Fee($)
New active substance	Submissions in support of a drug, excluding a disinfectant, that contains a medicinal ingredient not previously approved in a drug for sale in Canada and that is not a variation of a previously approved medicinal ingredient such as a salt, ester, enantiomer, solvate, or polymorph	348,606
Clinical or non-clinical data and chemistry & manufacturing data	Submissions based on clinical or non-clinical data and chemistry & manufacturing data for a drug that does not include a new active substance	176,569
Clinical or non-clinical data only	Submissions based only on clinical or non-clinical data for a drug that does not include a new active substance	82,410
Comparative studies	Submissions based on comparative studies (e.g., clinical or non-clinical data, bioavailability, pharmacokinetic and pharmacodynamic data) with or without chemistry & manufacturing data for a drug that does not include a new active substance	49,811
Chemistry & manufacturing data only	Submissions based only on chemistry & manufacturing data for a drug that does not include a new active substance	23,551
Published data only	Submissions based only on published clinical or non-clinical data for a drug that does not include a new active substance	19,530
Switch status from prescription drug to non-prescription drug	Submissions based only on data that support the modification or removing of a medicinal ingredient listed in Schedule F of the 「Food and Drug Regulations」	47,421
Labelling only	Submissions of labelling material (i.e. does not include supporting clinical or non-clinical or chemistry and manufacturing data)	3,174
Administrative submission	Submissions in support of a manufacturer or product name change	331
Disinfectants	Submissions and applications that include data in support of a disinfectant	4,392
Drug Identification Number (DIN) application - Labelling standard	Applications attesting to compliance with a labelling standard or Category IV Monograph for a drug that does not include clinical or non-clinical data or chemistry and manufacturing data	1,761

[Table 4] Fees for the Review of Drug Submissions

64) 「Guidance Document: Fees for the Review of Drug Submissions and Applications」, Nov-2015
65) Canada Gazette. Fees in Respect of Drugs and Medical Devices Regulations, Apr-2018

Ⅵ. References

Website

1. Health Canada: https://www.canada.ca/en/health-canada.html

Laws, regulations, and guidelines

1. Food and Drugs Act, 2017
2. Food and Drug Regulations, 2017
3. Natural Health Products Regulations, 2018
4. Draft Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements, 2016
5. Draft Guidance for Industry: Preparation of Comparative Bioavailability Information for Drug Submissions in the CTD Format, 2004
6. Guidance Document on the Import Requirements for Health Products under the Food and Drugs Act and its Regulations, 2010
7. Guidance Document: Drug Establishment Licences and Drug Establishment Licensing Fees, 2013
8. Guidance Document: Fees for the Review of Drug Submissions and Applications, 2015
9. Guidance Document: How to Interact with the Natural Health Products Directorate Electronically, 2016
10. Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs, 2017

11. Guidance Document: Labelling of Pharmaceutical Drugs for Human Use, 2015
12. Guidance Document: Notice of Compliance with Conditions (NOC/c), 2016
13. Guidance Document: Preparation of Drug Regulatory Activities in the "Non-eCTD Electronic-Only" Format, 2016
14. Guidance Document: Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format, 2012
15. Guidance Document: Product Monograph, 2016
16. Guidance Document: Submission of Risk Management Plans and Follow-up Commitments, 2015
17. Guidance for Clinical Trial Sponsors: Clinical Trial Applications, 2016
18. Guidance for Industry and Practitioners: Special Access Programme for Drugs, 2013
19. Guidance for Industry: Good Label and Package Practices Guide for Prescription Drugs, 2016
20. Guidance for Industry: Management of Drug Submissions, 2013
21. Guidance for Industry: Priority Review of Drug Submissions, 2005
22. Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites, 2009
23. Guideline: Good Manufacturing Practices (GMP) Guidelines for Active Pharmaceutical Ingredients (APIs), 2013
24. Guideline: Health Product Vigilance Framework, 2012
25. Guideline: Preparation of Drug Identification Number Submissions, 1995
26. Guideline: Risk Classification of Good Manufacturing Practices (GMP) Observations, 2012

Others

1. Frequently Asked Questions: Product Monographs Posted to the Health Canada Website, 2014
2. Notice: Annual Drug Notification Package is Now being Sent Electronically, 2012
3. Notice: Final Release – Part I: Health Professional Information and Part II: Scientific Information of the Guidance Document: Product Monograph, 2016
4. Notice: Updated Screening Criteria for Generic Drug Submissions, 2013
5. Policy: Health Products and Food Branch Inspectorate Import and Export Policy for Health Products Under the Food and Drugs Act and its Regulations, 2010
6. Policy Issues: Orphan Drug Policy, 1996
7. Questions and Answers: Yearly Biologic Product Reports (YPBR), 2008
8. Questions and Answers: Importation and Exportation, 2008

Appendix 1 CTD Modules in New Drug Submission

CTD Module No.	
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1.0.2	*Not applicable for paper submission*
1.0.3	*Copy of Health Canada-Issued Correspondence*
1.0.4	*Health Canada solicited Information*
1.0.5	*Meeting Information*
1.0.6	*Request for reconsideration documentation*
1.0.7	*General Note to Reviewer*
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1.2	Administrative Information
1.2.1	*Application Forms*
1.2.2	*Fee forms*
1.2.3	*Certification and Attestation Forms*
1.2.4	*Intellectual Property Information*
1.2.4.1	*Patent Information*
1.2.4.2	*Data Protection Information*
1.2.5	*Compliance and Site Information*
1.2.5.1	*Clinical Trial Site Information Form*
1.2.5.2	*Establishment Licensing*
1.2.5.3	*Good Clinical Practices*
1.2.5.4	*Good Laboratory Practices*
1.2.5.5	*Good Manufacturing Practices*
1.2.5.6	*Good Pharmacovigilance Practices*
1.2.5.7	*Other Compliance and Site Information Documents*
1.2.6	*Authorization for Sharing Information*
1.2.7	*International Information*
1.2.8	*Post-authorization Information*
1.2.9	*Other Administrative Information*
1.3	Product Information
1.3.1	*Product Monograph*
1.3.2	*Inner and Outer Labels*
1.3.3	*Non-Canadian Labelling*
1.3.4	*Investigator's Brochure (for CTAs only)*
1.3.5	*Reference Product Labelling*
1.3.6	*Certified Product Information Document*
1.3.7	*Look-alike/Sound-alike Assessment*
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1.3.8.1	*Pharmacovigilance Information*
1.3.8.2	*Risk Management Plan*
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1.3.8.4	*Other Pharmacovigilance Information*

CTD Module No.	
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1.4.1 *1.4.2* *1.4.3*	*Protocol Safety and Efficacy Assessment Template – CTA (for CTAs only)* *Comprehensive Summary: Bioequivalence* *Multidisciplinary Tabular Summaries*
1.5	Environmental Assessment Statement
1.6	Regional Clinical Information
1.6.1 *1.6.2* *1.6.3* *1.6.4*	*Comparative Bioavailability Information* *Company Core Data Sheets* *Priority Review request* *Notice of Compliance with Conditions*
1.7	Clinical Trial Information
1.7.1 *1.7.2* *1.7.3* *1.7.4*	*Study Protocol* *Informed Consent Forms* *Canadian Research Ethics Board Refusals* *Information on Prior Related Applications*
1.A	Appendix
1.A.1	*Electronic Review Package++*
2	**CTD Summaries**
2.1 2.2 2.3 2.4 2.5 2.6 2.7	Overall CTD Table of Contents (Modules 2 to 5) Introduction Quality Overall Summary Nonclinical Overview Clinical Overview Nonclinical Written and Tabulated Summaries Clinical Summary
3	**Quality**
3.1 3.2 3.3	Module 3 Table of Contents Body of Data (including Regional requirements) Literature References
4	**Nonclinical Study Reports**
4.1 4.2 4.3	Module 4 Table of Contents Study Reports Literature References
5	**Clinical Study Reports**
5.1 5.2 5.3 5.4	Module 5 Table of Contents Tabular Listing of Clinical Studies Clinical Study Reports Literature References

Appendix 2 Drug Review Notice Types[66]

1) Screening Deficiency Notice (SDN)

If deficiencies are identified during screening of original information and material, the sponsor will be issued an SDN identifying the deficiencies. The sponsor will be required to submit all of the requested information and material identified in the SDN, within 45 calendar days from the date of request. If the sponsor fails to provide all requested information within 45 calendar days, or the submitted information is incomplete, deficient or contains unsolicited information, the original information and material will be rejected and a Rejection Letter will be issued by Health Canada.

2) Clarifax/Clarimail

The purpose of a Clarifax/Clarimail is to expand on, add precision to or reanalyze existing information or data in the submission. Clarifaxes/Clarimails do not contain requests for new data, such as, new clinical and/or preclinical information, including new bioavailability data not previously submitted. During the screening or review of the submission, including the label review, a Bureau/Centre may seek clarification of specific information in the submission. Requests will be solicited by fax or email and must be responded to in writing in CTD format. The sponsor will be advised that the solicited information must be submitted within 15 calendar days (2 calendar days for Priority Review requests) from the date of the request.

3) Notices of Deficiency (NOD)

If deficiencies and/or significant omissions, that would preclude continuing the review, are identified during the review of a submission a NOD will be issued. The difference between a Notice of Non-compliance (NON) and NOD are: the review of the submission is not complete when a NOD is issued while the review is complete when a NON is issued. Only one NOD per submission will be issued. Review of the submission will stop on the date of the NOD. For NDSs, SNDSs, ANDSs, and SANDSs the sponsor will be given 90 calendar days, or such time as the Bureau/Centre Director and sponsor may agree upon, to submit all of the solicited information.

66) 「Guidance for Industry: Management of Drug Submissions」, Dec-2013

4) Notices of Non-compliance (NON)

After the comprehensive review of a submission is complete, a NON will be issued if the submission is deficient or incomplete in complying with the requirements of the 「Food and Drugs Act」 and 「Regulations」. The deficiencies identified in all parts of the review will be specified. Only one NON per submission will be issued. Review of the submission will stop on the date of the NON. For all new drug submissions, sponsors will be given 90 calendar days, or such time as the Directorate and sponsor may agree upon, to submit all of the solicited information. For DIN submissions, the sponsor will be given 45 calendar days to submit all the solicited information.

5) Notice of Compliance (NOC)

This decision means that the submission has been reviewed and found to be acceptable. The product will be able to proceed to marketing.

6) Notice of Compliance with Conditions-Qualifying Notice (NOC/c-QN)[67]

An NOC/c-QN will be issued by the Director of the responsible reviewing Bureau/Centre upon completion of a review, should a submission be determined to qualify for further consideration under the NOC/c policy. The NOC/c-QN will indicate that the submission qualifies for an NOC, under the NOC/c policy, as well as outline the additional clinical evidence to be provided in confirmatory studies, post-market surveillance responsibilities, and any requirements related to advertising, labelling, or distribution.

67) 「Guidance Document: Notice of Compliance with Conditions (NOC/c)」, Sep-2016.

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※ If there is any inquiry or comment on this document, please contact the APEC Harmonization Center.

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