Health Canada Santé Canada

Canada

The Canadian Regulatory Environment: Organization, Regulations, and Flexibilities in Implementation

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Tel Aviv

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Health Canada

YOUR HEALTH AND SAFETY... OUR PRIORITY.

Contents

- Organisation
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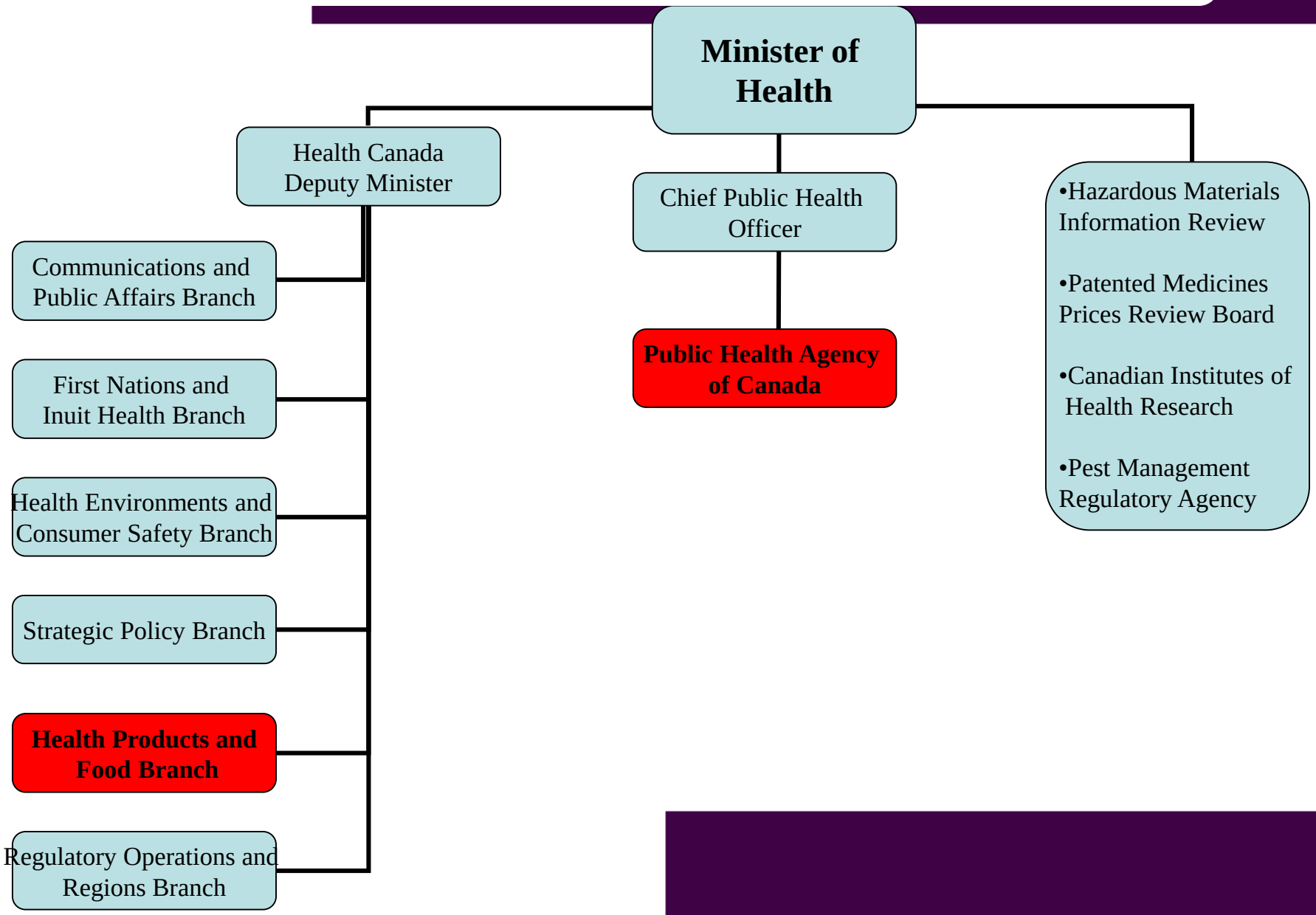
Health Canada

- Federal department responsible for helping Canadians maintain and improve their health, while respecting individual choices and circumstances

- Responsible for maximizing the safety and effectiveness and minimizing the risks associated with therapeutic products

- Includes regulatory review and authorization of drug clinical trial submissions and applications for marketing under authority of Food and Drugs Act and Regulations, as well as ongoing risk management

Organizational Structure of the Canadian Health Ministry



Health Products and Food Branch

- HPFB's mandate is to take an integrated approach to managing 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; and,

- promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.

Products Regulated by HPFB

- Pharmaceuticals (prescription, non-prescription, brand name and generics)
  - Human and Veterinary uses
- Biological drugs (vaccines, recombinant DNA drugs, blood and its derivatives)
- Radiopharmaceuticals
- Medical Devices
- Natural Health Products
  - Traditional herbal medicines
  - Other Herbals, Homeopathic products
- Disinfectants for use on medical instruments, hospital and food preparation surfaces

Canada's Regulatory Framework
The Food and Drugs Act and Regulations

Canada has a strong regulatory framework for therapeutics which has its basis in the provisions of the Food and Drugs Act

- the purpose of the Act is to prevent health fraud and consumer deception and ensure consumer and purchaser safety

Seven sets of regulations under the Act:

- Food & Drugs,
- Cosmetics,
- Medical Devices,
- Semen for Assisted Conception
- Natural Health Products
- Cells, Tissues and Organs for Transplantation
- Blood

Drug Regulations (Part C) provide for three lines of intervention:

- Product Review and Standards
- Manufacturing Controls and Establishment licensing
- Conditions of Sale

The Food and Drug Regulations

Part C deals with drugs that are pharmaceuticals, biologics and radiopharmaceuticals

- Division 1 - General Section
- Division 1A - Establishment Licensing
- Division 2- Good Manufacturing Practices
- Division 3 - Radiopharmaceuticals
- Division 4 - Biologics
- Division 5 - Clinical Trials
- Division 6 - Canadian Standard Drugs
- Division 7 - Canada's Access to Medicines Regime
- Division 8 - New Drugs
- Division 9 - Analgesics

Definition of “Drug” in the Act

”….. includes any **substance or mixture of substances** manufactured, sold or represented for use in:

- the **diagnosis, treatment, mitigation or prevention** of a disease, disorder, abnormal physical state, or the symptoms thereof, in man or animal,
- **restoring, correcting or modifying** organic functions in **man or animal**, or
- **disinfection** in premises in which food is manufactured, prepared or kept.“

The regulations further define “New Drug” as that which:

- has not been sold in Canada for **sufficient time and in sufficient quantity** to establish its safety and efficacy or
- new **combination of two or more drugs** or
- new claim or a **condition of use as a drug**, including dosage, route of administration, or duration of action

Marketing Authorization Overview

Human Trials

Clinical trial application (CTA) required if trial done in Canada

New Drug Submission

Complete quality, safety and efficacy data to support licensure

Notice of Compliance/Drug Identification Number/Establishment License Issued

Post-Market

Surveillance

Lot release (biologics)

Filing of supplements for significant changes for review and authorization

Compliance enforcement and investigation

Types of Submissions

- Clinical Trial Application (CTA) and Amendments
- New Drug Submission (NDS)
- Abbreviated New Drug Submission (ANDS)
- Supplemental New Drug Submission (SNDS)
- Notifiable Change (NC)

Clinical Trial Regulations for Drugs

Current regulations under Part C, Division 5 have been in effect since September 1st, 2001, and were implemented with two overarching objectives:

- strengthen protections for human research subjects
- increase R & D investment in clinical trials in Canada

Regulations incorporate essential elements of Good Clinical Practices

- Sound research protocol
- Informed consent of research subjects
- REB approval and continuing oversight
- Appropriate qualifications of investigator and staff
- Monitor and report serious, unexpected, adverse drug reactions
- Maintain accurate records

Regulations give the Minister clear authority to reject, suspend or cancel the authorization of a clinical trial

Clinical Trial Application

- Covering letter
- HC/SC form 3011
- Attestation
- Protocol and Informed Consent Form
- Investigator’s Brochure or Product Monograph
- Protocol Safety and Efficacy Assessment Template
- Clinical trial site information form (CTSI)
- REB refusals
- Chemistry and manufacturing templates
- Supporting chemistry and manufacturing information

CTA Review by Health Canada

The reviewers assess all the information provided by the sponsor, including:

- Scientific merit: rationale, study design, population, dosage regimen, safety and efficacy variables
- Sufficient information to support the safety of the drug for the purposes of the trial
- Adequate communication of potential risks and anticipated benefits to trial subjects
- Acceptable chemistry and manufacturing information

Review Outcome

- 30 calendar day review period (no holds permitted)
- 30 day period is a default, meaning if no objection from Health Canada is received, trial may proceed
- No-Objection-Letter (NOL)
- Not-Satisfactory Notice (NSN)

Post authorization requirements, including reporting of adverse drug reactions

Clinical trial site inspection program

Pre-submission meetings

Highly recommended both for clinical trials and for NDSs or SNDSs!

Benefit-risk assessment in the context of clinical trial review

- Assessing benefit/risk involves:
  - Analysis of unmet medical need and disease characteristics
  - Analysis of data accumulated through product development
- Both the regulator and the sponsor assess benefit/risk continuously
- Evaluate potential risks and weigh the probability of risk occurring and the magnitude of harm that may result
- Judge whether the anticipated benefit (new knowledge or improved health for the research subjects) justifies inviting any person to undertake the risks
- Distinguish the risk of research from the risk of therapies the subjects would receive even if not participating in research
- Evaluate the available clinical and nonclinical information

Risk minimization

- Determine that the risks are reasonable in relation to the benefits to subject, and the importance of the knowledge to be gained
- Assure that potential subjects will be provided with an accurate and fair description of the risks or discomforts and the anticipated benefits (during consent)
- Respect the subject’s privacy
- Research Ethics
- Stopping rules
- Data Safety Monitoring Boards (DSMB)

New Drug Submissions (NDS)

No person shall sell or advertise a new drug unless:

- (a) the manufacturer has filed with the Minister a New Drug Submission or an Abbreviated New Drug Submission relating to the new drug that is satisfactory to the Minister;
- (b) the Minister has issued a Notice of Compliance (NOC) for the drug
- (c) the Notice of Compliance has not been suspended
- (d) the manufacturer has submitted to the Minister specimens of the final version of any labels, including package inserts, product brochures and file cards, intended for use in connection with that new drug

Summary of NDS Requirements

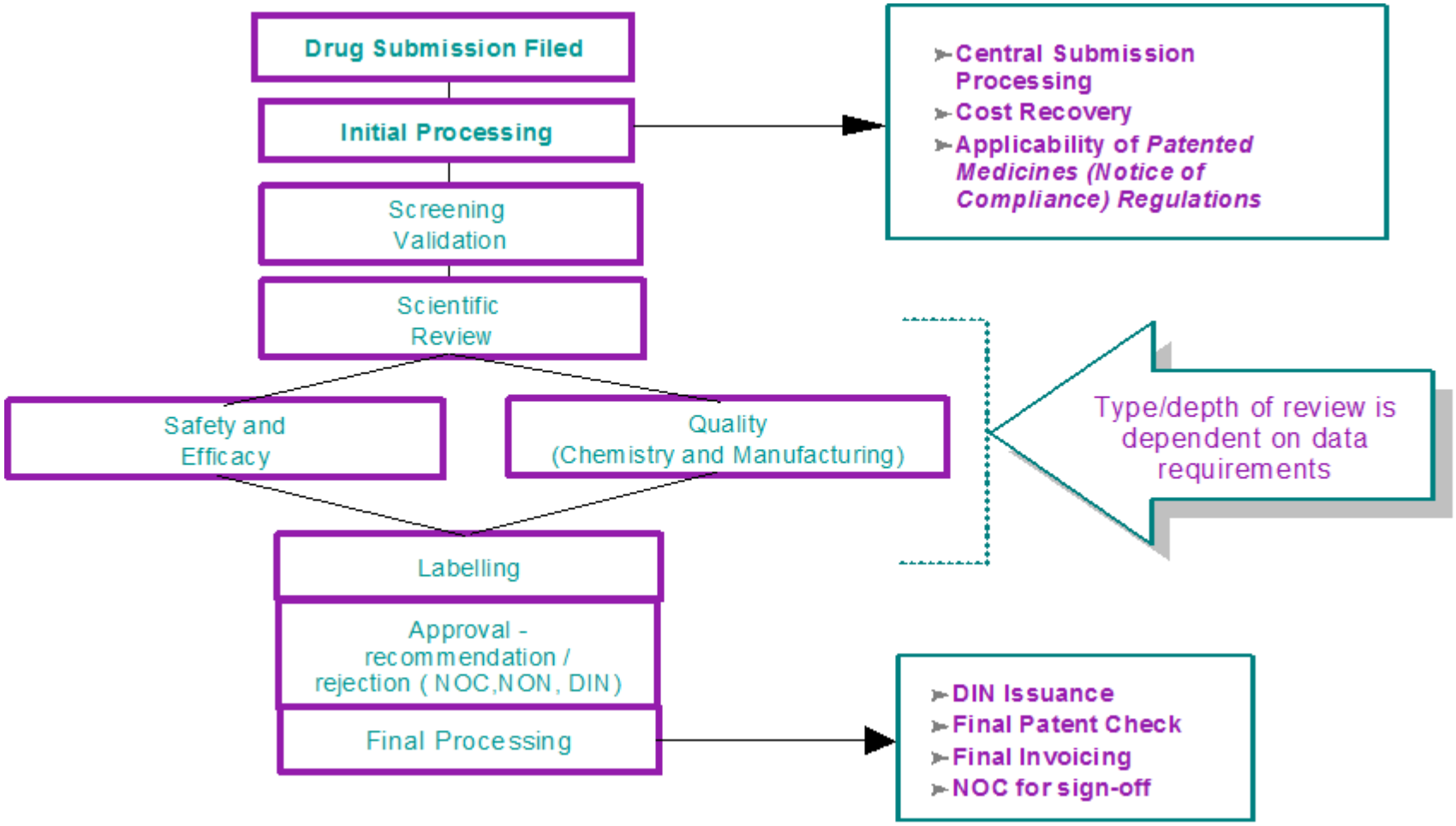
- A new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following:

- description of drug, proper name or its common name if no proper name;
- brand name of the new drug or the identifying name or code
- list of ingredients stated quantitatively, and specifications for each
- description of plant and equipment used in manufacture, preparation and packaging;
- details of method of manufacture and controls used in manufacture, preparation and packaging
- details of tests to applied to control the potency, purity, stability and safety of the new drug;
- evidence to establish safety
- substantial evidence of clinical effectiveness draft labels;
- representations to be made respecting: recommended route of administration; proposed dosage, claims to be made, and contra-indications and side effects
- a description of the dosage form in which it is proposed that the new drug be sold;
- evidence that all test batches used in any studies conducted in connection with the submission were manufactured and controlled in a manner that is representative of market production;

Biologic vs Pharmaceutical

- **The same regulatory process is used for the filing and review of biologics and pharmaceuticals, however, some additional requirements apply to biologics**:
  - **Pre-approval on-site inspection by quality review staff**
    - Product specific evaluation conducted at site of manufacture (drug substance or drug product) to assess premises where drug manufactured, process, conditions and control of manufacture and conformity with information submitted
    - Scheduled prior to the issuance of an NOC
  - **More information on manufacturing facility**
  - **Samples for consistency testing in Health Canada labs**
    - Generally samples from 3-5 consecutively manufactured lots are tested to ensure consistency. These lots may be released for sale once NOC is issued.

New Drug Review Process



Post-Market Changes

- Following the issuance of a Notice of Compliance by Health Canada, changes to marketed drugs are grouped into 4 categories based on the significance of the change and therefore the potential impact on safety and efficacy

- Changes grouped in the following categories require the filing of a submission and authorization by Health Canada prior to implementation:
- Level 1: Supplements
- Level 2: Notifiable Change

Priority Review Policy

Policy applies to NDSs and SNDSs for serious, life-threatening or severely debilitating disease for which there is substantial evidence that the drug provides:

- effective treatment of a disease for which no drug is available; OR
- offers a significant increase in efficacy and/or significant decrease in risk over existing therapies for a disease that is currently not adequately managed.

Manufacturer submits a written request to Director of Bureau (Clinical Assessment Package) Application includes:

- Generic name and brand name
- Indication
- Synopsis of data
- Description of disease condition and role of product

Director gives a response in 30 days. Company then has 60 days to submit.

Notice of Compliance with Conditions Policy

Policy applies to NDSs or SNDSs for serious, life-threatening or severely debilitating diseases or conditions for which there is promising evidence that the drug can provide:

- effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada; OR

- a significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada.

Abbreviated New Drug Submission

Applies to products (typically generics) that are:

- Pharmaceutically equivalent
- Bioequivalent to Canadian Reference Product
- Given via the same route of administration as Canadian Reference Product
- Sold for the same conditions of use as Canadian Reference Product
- NOC for an ANDS states the Canadian reference product and constitutes a “declaration of equivalence” for the new product.
- This is very important from a provincial reimbursement perspective.

Biosimilars

A biosimilar is a biologic drug that:

- enters the market subsequent to a version previously authorized in Canada, and with demonstrated similarity to that reference biologic drug;
  - Similarity depends on ability to characterize. Therefore with current technology only biologics containing well-characterized proteins derived through modern biotechnological methods will qualify as SEBs
- relies in part on prior information regarding safety and efficacy due to the demonstration of similarity to the reference biologic drug;

Canadian Regulatory Approach for Biosimilars

- Biosimilars are regulated as new biologic drugs in Canada; they are subject to the Food and Drugs Act and Part C, Division 8 of the Food and Drug Regulations just like other new biologic drugs.

- Flexibility under existing legislation allows for the regulation of biosimilars using the concept of similarity.

- The demonstration of similarity is based upon the totality of evidence and is the basis for accepting a reduced non-clinical and clinical data package.
  - analytical testing, biological assays, and non-clinical and clinical data.

- A guidance document was published in 2010 to communicate submission requirements to biosimilar sponsors. The document is under revision to reflect experience gained by Health Canada over time.

Fundamental Principles of Biosimilars

- Patient safety is paramount
- Biosimilars are not “generic” drugs:
  - Biologics are derived from living organisms, large in size and highly variable;
  - Two different versions of a biologic can never be considered identical
  - The existing regulatory pathway for generics cannot be used for biologics
  - Biosimilars are new drugs and will be regulated as such however some clinical and non-clinical data requirements may be reduced
  - Science-based approach

Guidance for Sponsors: Submission and Information Requirements for Subsequent Entry Biologics (Biosimilars)

- Acceptance of a reduced non-clinical/clinical data package hinges on demonstrated similarity between the biosimilar and a biologic drug already authorized for sale in Canada (Reference Biologic Drug or RBD)
- The indications granted to a biosimilar shall be based on data provided by the sponsor.
- Biosimilars are subject to the Food and Drug Regulations (Data Protection), Patented Medicines (Notice of Compliance) Regulations, and the Patent Act
- Authorization of a biosimilar is not a declaration of equivalence to the RBD
- Once a Notice of Compliance is issued, the biosimilar is a new drug and regulated accordingly
- A Risk Management Plan required prior to issuance of authorization.

Performance Targets for Submissions

		Calendar days
Processing		10 days
Screening	: priority	25 days
	: non-priority	45 days
NDS	: priority	180 days
	: non-priority	300 days
SNDS	: clinical	300 days
	: C & M only	180 days
ANDS		180 days

- Health Canada's commitment: 90% of all submissions will have a decision by the target date
- Similar time frame to EU but no hold provision

How flexible is Health Canada?

In terms of flexibility there is a difference between Recommendations, Guidelines and Regulations

Recommendations: can be made by professional associations or public health organizations and do not have regulatory status

Guidelines: the word “should” is often used, which means that, with proper justification, a different approach may be used

- For example:…sections of the product monograph in the order that they should appear.

Regulations: whenever the word “shall” is used, the requirement must be fulfilled

- For example: C08.001(2)A new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, including the following…

Example: regulatory requirements for NDS

- According to Division 8

A new drug submission shall contain sufficient information and material to enable the Minister to assess the safety and effectiveness of the new drug, I including the following:

(g) detailed reports of the tests made to establish the safety of the new drug for the purpose and under the conditions of use recommended;

(h) **substantial** evidence of the clinical effectiveness of the new drug for the purpose and under the conditions of use recommended;

However…

…there is some flexibility

- Safety and efficacy are assessed in the context of the disease (is it a rare disease? How serious is it? Are there any other treatments for it?) and the population who will use the product
- There is always a benefit-risk consideration: for example, a prophylactic vaccine given to healthy people and a drug indicated for the treatment of a deadly disease for which there is no cure will have diferent level of safety and efficacy data
- There are circumstances when third party data may be acceptable, however this has to be discussed and agreed upon at a pre-submission meeting
- In clinical trials, the benefit-risk profile may change with the different phases of development

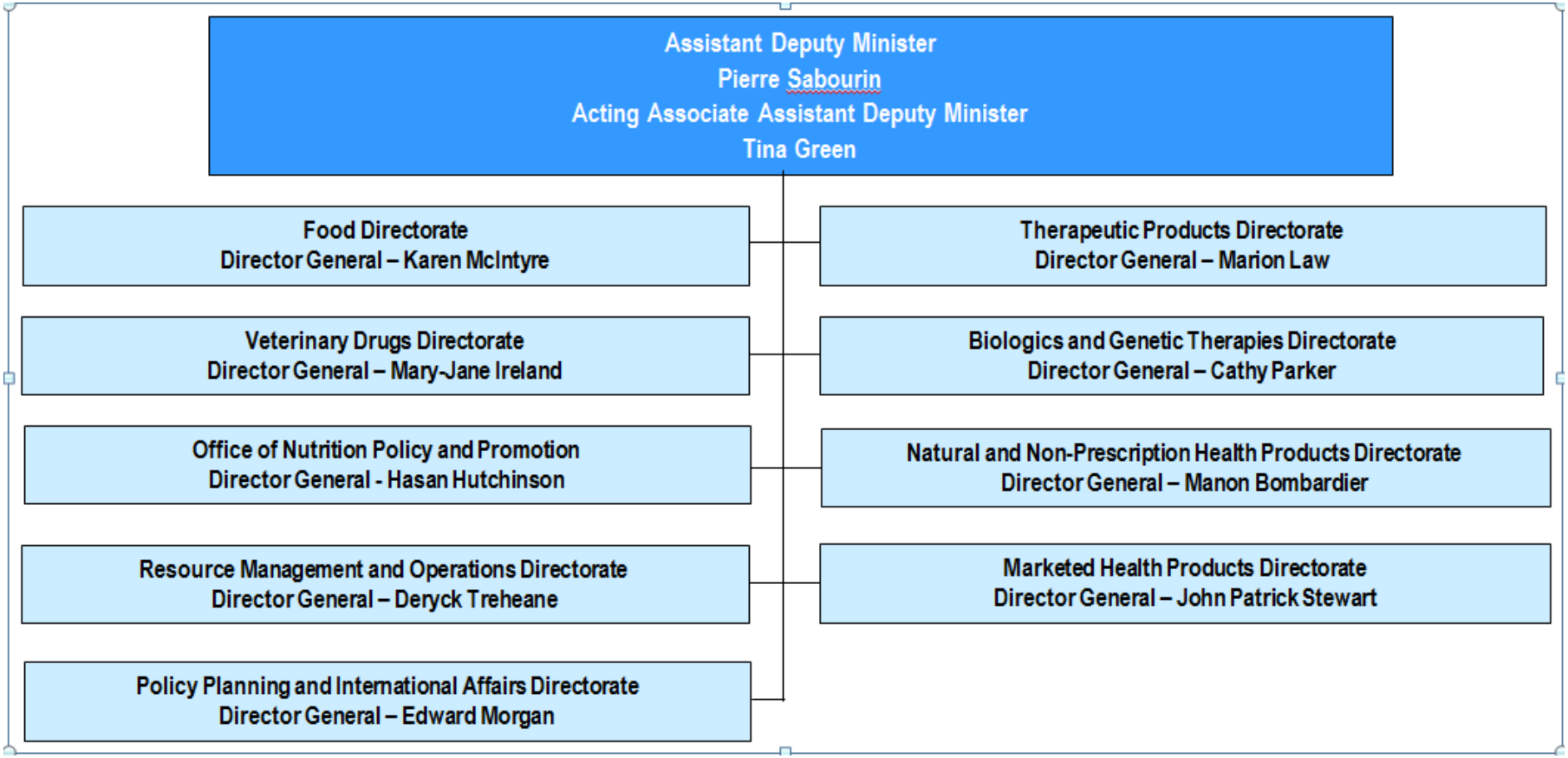
Guidance Documents

Management of Drug Submissions Guidance
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/mgmt-gest/mands_gespd-eng.php
Common Technical Document
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ctd/index-eng.php
Submission Evaluation Fee Guide
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/fees-frais/fee_frais_guide-eng.php
Notice of Compliance with Conditions
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/compli-conform/index-eng.php
Preparation of DIN Submission
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/pre_din_ind-eng.php
Priority Review
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/priorit/index-eng.php
Biologics Lot Release
http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/lot/index-eng.php
Clinical Trials e-Manual
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_intro-eng.php
Other/Relevant Information related to Clinical Trials
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/index_e.html
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/qtqtc/index_e.html
Post Notice of Compliance (NOC) Changes
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/postnoc_change_apresac/noc_pn_saf_ac_sa_inn-eng.php
Drug Submissions Relying on Third-Party Data (Literature and Market Experience)
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/srtd_pfdt_gd_ld-eng.php

Thank you!

ADDITIONAL SLIDES

ORGANISATIONAL STRUCTURE:
The Health Products and Food Branch (HPFB)



Biologics and Genetic Therapies Directorate

- Director General's Office:
  - Advisors
  - Office of Business Integration and Risk Management
    - Planning, Administration , Risk, Quality Management, etc.
  - Office of Policy and International Collaboration
  - Office of Regulatory Affairs
- Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics
- Centre for Biologics Evaluation
  - Includes Research

Level 1 Supplements

- A Level 1 Supplement type change is defined as those changes to a drug that are significantly different and have the potential to impact the safety, efficacy, quality and/or effective use of the drug
- e.g. new indication, change in dosage, new formulation, new manufacturing facility

- Level 1 Supplement changes require the filing of a Supplemental New Drug Submission (SNDS)

- The change may not be implemented until a Notice of Compliance is issued

Level 2 Notifiable Changes

- A Level 2 Notifiable Change is defined as changes to a drug that are not considered significantly different but still have the potential to impact the safety, efficacy, quality and/or effective use of the drug
- e.g. updates to the Product Monograph regarding adverse events, addition of new product-contact equipment used in a critical manufacturing process step

- Level 2 Notifiable Changes require the filing of a Notifiable Change (NC) Submission
- 90-120 day review target

NOC/c - Requirements

- Sponsor must provide a written commitment to pursue confirmatory studies acceptable to Health Canada
- Sponsor must agree to enhanced post-market surveillance and reporting
- Conditions” must be clearly reflected and highlighted in the PM and all labelling
- Restrictions on advertising and/or distribution
- Additional educational material, Dear Health Care Professional Letters, Fact Sheets etc.

Biosimilars authorized in Canada (as of September 2016)

Biosimilar	Reference Biologic Drug	Therapeutic area	Date of NOC
Omnitrope (Somatropin – Human Growth Hormone)	Genotropin	Growth Hormone Deficiency in Children and Adult Growth Hormone Deficiency	April 20, 2009
Omnitrope	Genotropin	Additional indications for Small for Gestational Age, Idiopathic Short Stature and Turner Syndrome	May 8, 2015
Inflectra (Infliximab –Monoclonal Antibody)	Remicade	Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis and Plaque Psoriasis	January 15, 2014
Inflectra	Remicade	Additional indications for Adult Crohn's disease, including fistulising Crohn's disease and adult ulcerative colitis	June 10, 2016

Biosimilars Challenges

- **Patient and Health Care Provider Confidence**
  - Perception that biosimilars have less rigid pre and post market data requirements
  - As a new category of drug products there is a need to educate on their safety and efficacy
- **Naming**
  - Controversy over whether biosimilars should have unique identifier
  - No international consensus on naming scheme.
  - Role of the WHO Biological Qualifier?
- **Rapidly Evolving Field**
  - Ongoing challenge of policy/regulatory approaches keeping pace with science.
  - Collaboration with other regulators (IPRF Biosimilars WG, Biosimilars Cluster) and participation in WHO guideline drafting groups extremely helpful.
  - Regular review of biosimilars guidance document.
- **Interchangeability**
  - Biosimilars are not linked to their reference products in the way of generic pharmaceuticals. Regulatory authorization by Health Canada is not a declaration of equivalence.
  - Pressure from various stakeholders to provide direction.
  - Designation of a drug as interchangeable is under the purview of the provinces/territories.

Research Ethics

- Research ethics is specifically interested in the analysis of ethical issues that are raised when people are involved as participants in research.
- There are three objectives in research ethics:
  - The first and broadest objective is to protect human participants.
  - To ensure that research is conducted in a way that serves interests of individuals, groups and/or society as a whole
  - To examine specific research activities and projects for their ethical soundness, looking at issues such as the management of risk, protection of confidentiality and the process of informed consent.
- In Canada, current debates and challenges in research ethics include the changing notions of what constitutes research and therefore requires formal ethics review, the oversight and monitoring of the work of Research Ethics Boards (known as Institutional Review Boards, in the U.S.) at federal and provincial levels, the jurisdiction of Research Ethics Boards in academic, clinical and corporate settings, the increasing multidisciplinarity of research collaborations and pursuits and challenges created by rigorous federal and provincial privacy legislation.

Data Safety Monitoring Boards (DSMB)

- Independent committee established by sponsor
- Made up of individuals with pertinent expertise:
- Biostatistics specialist who have expertise in clinical trial design
- Relevant medical specialists
- All of whom should be known for their integrity
- Review accumulating data at predetermined intervals
  - Safety
  - Efficacy

Functions of the DSMB

- To advise Trial Sponsors and/or their Steering committees on the ongoing validity and scientific merit of a trial
- Recommend modifications to a study protocol, the continuation of a study its temporary stop or permanent discontinuation
- Perform sequential benefit-risk assessment
- Help validate the integrity of the data

Benefit/Risk Phase I Clinical Trials

- Healthy volunteers:
- Benefits: societal benefit only (monetary benefit is not taken into account in regulatory decision)
- Risks
- Drug type and target
- Potential toxicity based on pre-clinical studies
- Drug product quality
- Proposed starting dose and dose-escalation method
- Route of administration
- Risk mitigation measures

Benefit/Risk –Phase II

Benefits: societal benefit; potential benefit to trial subjects

Risk mitigation measures

- Patient population
- Potential toxicity based on pre-clinical studies
- Safety data from phase I studies
- Changes in drug product quality
- Proposed phase II starting dose and dose-range
- Study design and endpoints
- Duration of trial
- Sample size

Benefit/Risk – Phase III

Benefits: societal benefit; potential benefit to trial subjects

Risk mitigation measures

- Patient population
- Safety data from phase I and II studies
- Changes in drug product quality
- Proposed dose or dosage regimen
- Study design and endpoints
- Statistical plan
- Duration of trial
- Tests and procedures