Health Canada Santé Canada

Therapeutic Products Directorate

Health Products and Food Branch

Direction des produits thérapeutiques

Direction générale des produits de santé et des aliments

Review and Approval of New Drugs for Infectious Diseases in Today's Climate

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BGIVD,
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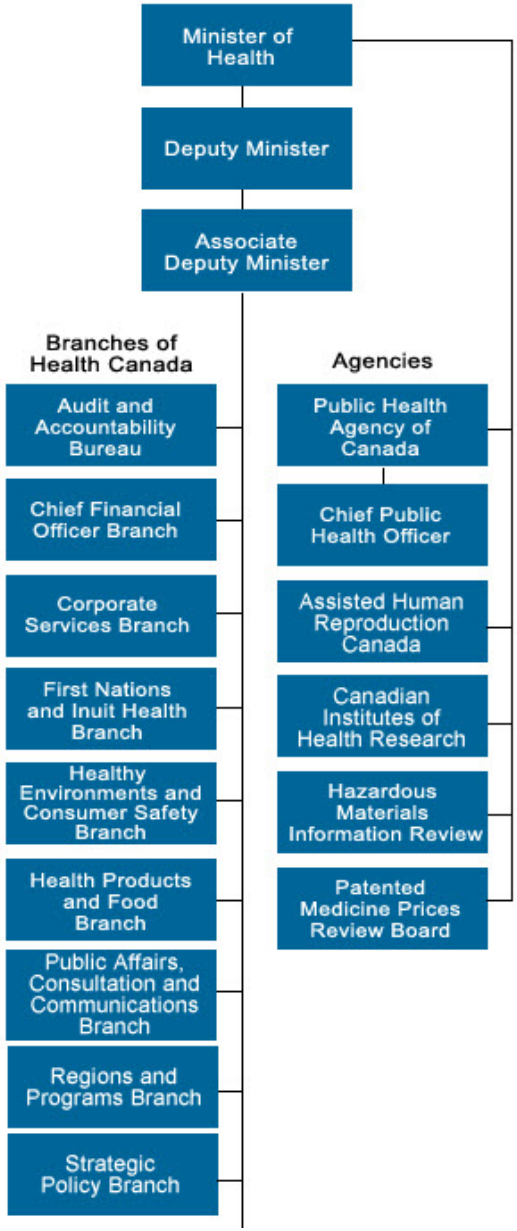
Canada

Objectives

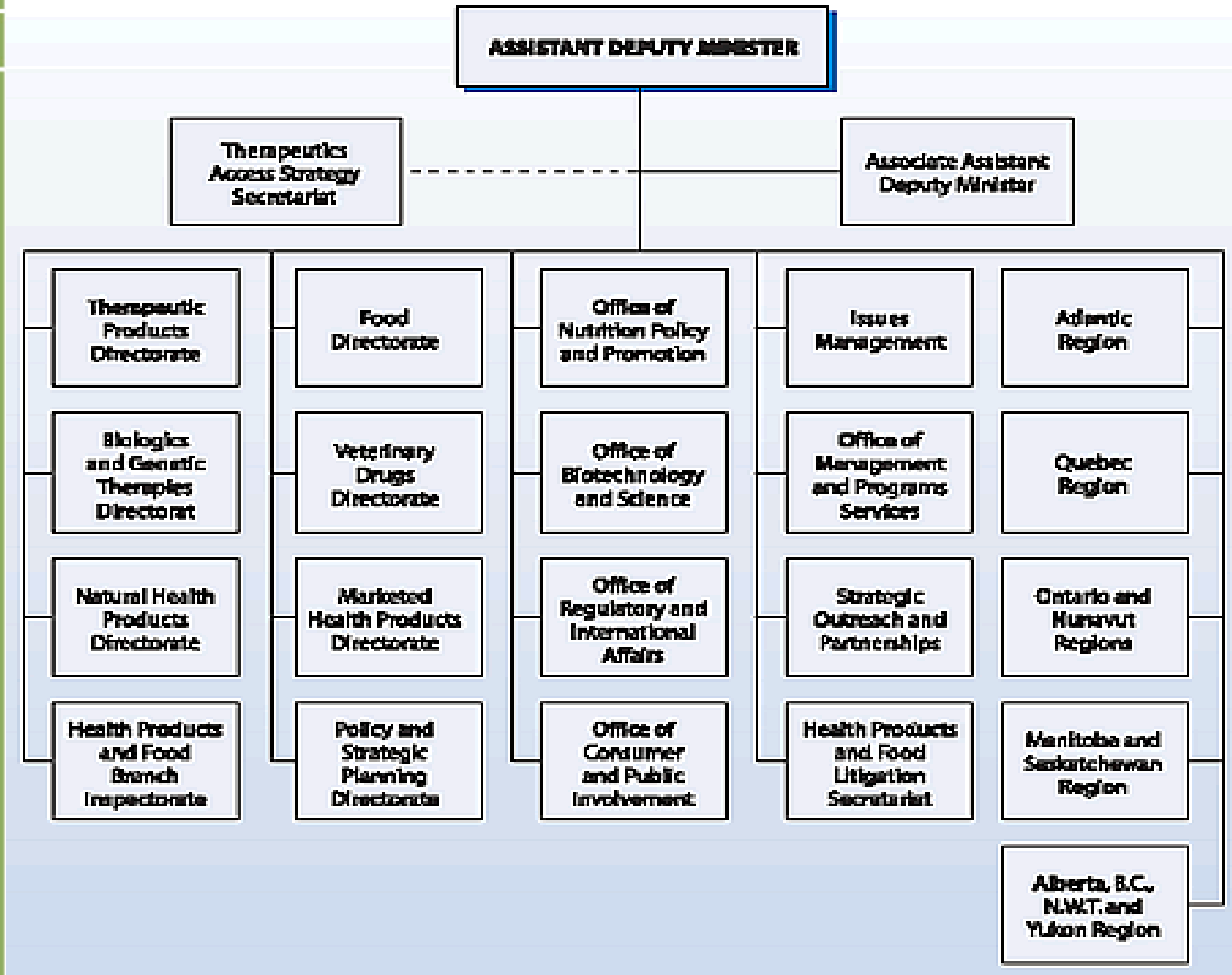
- To understand the organizational structure (including the legal basis) under which the drug approval process is carried out
- To understand the process of evaluating the efficacy and safety of anti-infective drugs before, during and after licensure
- To understand the roles of physicians, the pharmaceutical industry and the government in the process

Topics to be addressed

- Structure of Health Canada (organizational)
- The Regulatory framework
- The New Drug Submission (NDS) content
- NDS review consideration
- Anti-Infective drugs in Today's climate


Minister of Health
Deputy Minister
Associate Deputy Minister
Branches of Health Canada
Audit and Accountability Bureau
Chief Financial Officer Branch
Corporate Services Branch
First Nations and Inuit Health Branch
Healthy Environments and Consumer Safety Branch
Health Products and Food Branch
Public Affairs, Consultation and Communications Branch
Regions and Programs Branch
Strategic Policy Branch
Agencies
Public Health Agency of Canada
Chief Public Health Officer
Assisted Human Reproduction Canada
Canadian Institutes of Health Research
Hazardous Materials Information Review
Patented Medicine Prices Review Board

HPFB Org. Chart

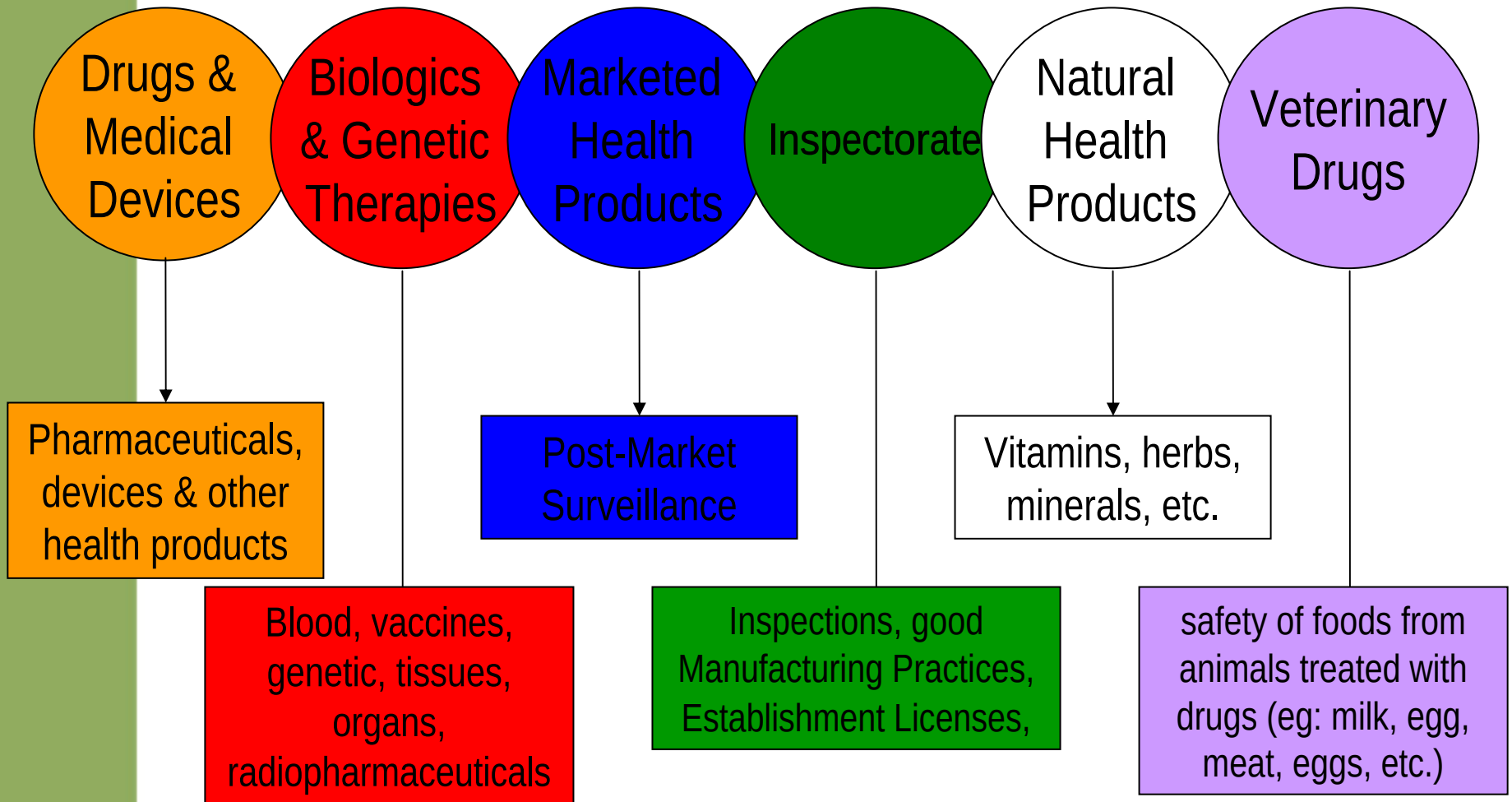


HPFB

- **Health Products and Food Branch activities are carried out through offices in the National Capital Region and five regional offices: Atlantic, Quebec, Ontario, Manitoba-Saskatchewan and Western.**

- Biologics and Genetic Therapies Directorate
- Food Directorate
- Health Products and Food Branch Inspectorate
- Marketed Health Products Directorate
- Natural Health Products Directorate
- Office of Consumer and Public Involvement
- Office of Management and Program Services
- Office of Nutrition Policy and Promotion
- Departmental Biotechnology Office
- Office of the Assistant Deputy Minister
- Policy, Planning and International Affairs Directorate
- Regional Operations
- Therapeutic Products Directorate
- Veterinary Drugs Directorate

Health Products and Food Branch (HPFB) Responsibilities for Human Drugs



Therapeutic Products Directorate

TPD consists of 12 offices and bureaux:

- Director General's Office
- Medical Devices Bureau
- Submission and Information Policy Division
- Office of Business Transformation
- Office of Clinical Trials
- Office of Patented Medicines and Liaison
- Office of Risk Management
- Bureau of Policy, Science and International Programs
- Bureau of Cardiology, Allergy and Neurological Sciences
- **Bureau of Gastroenterology, Infection and Viral Diseases**
- Bureau of Metabolism, Oncology and Reproductive Sciences
- Bureau of Pharmaceutical Sciences

BGIVD

- Gastroenterology Division
- Division of Anti-Infective Drugs
- AIDS and Viral Diseases Division
- Disinfectant Unit
- Non-prescription drugs

BGIVD

- AIDS and Viral Diseases Division

  Antiviral drugs, anti-fungal and antibacterial drugs used for the treatment of opportunistic infections in immune compromised patients

- Division of Anti-Infective Drugs

  Antibiotics (including anti-tuberculosis agents), antifungal, and anti-parasitic drugs

Topics to be addressed

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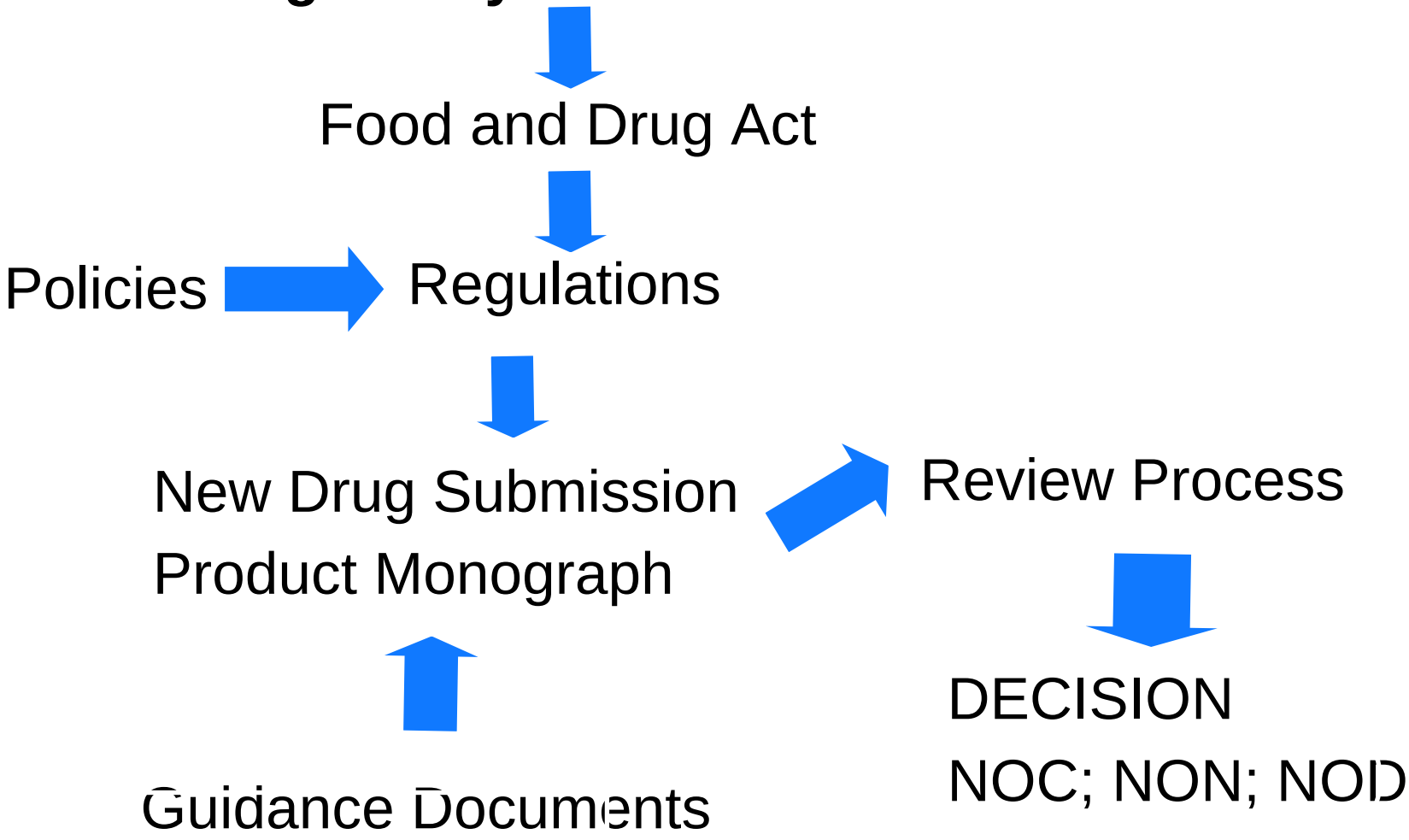
Federal Legislation and Guidance for Drugs

- Food and Drugs Act and Regulations
  - ✓ Governs the safety, effectiveness and quality of *drugs* and *medical devices* available to Canadians.
- Patented Medicines (NOC) Regulations
- Financial Administration Act
  - ✓ (Fees for review - cost recovery)
- Access to Information and Privacy Act
- Controlled Drugs and Substances Act
  - ✓ Governs Narcotic & Controlled Drugs
- Policies and Guidelines (including International Guidelines - ICH) in support of the Act and Regulations

The Regulatory Framework



Definition of a Drug

"…. 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
- disinfections in premises in which food is manufactured, prepared or kept.“
  - **allows for flexibility and interpretation**

New Drug Submission (NDS)

- A New Drug Submission (C.08.002) shall include:
  - Description of the new drug and its proper name and brand name
  - Information dealing with manufacturing and quality control
  - Detailed reports describing non-clinical and clinical studies that establishes safety
  - Substantial evidence of the clinical effectiveness
  - Draft of proposed labelling, including the Product Monograph

Product Types Regulated as “Drugs”

- Pharmaceuticals (prescription, non-prescription, generic)
- Biological drugs (vaccines, recombinant drugs, blood)
- Radiopharmaceuticals
- Natural Health Products (Transition to NHPD, January 1st, 2004)
  - Homeopathic products
  - Traditional herbal medicines
  - Other Herbals

  eg: Antiperspirant, Toothpaste with fluoride – drugs before the new NHP Regulations
- Disinfectants for use on medical instruments, hospital and food preparation surfaces
- Veterinary Drugs

Definition of a "New Drug"

- A ***New Drug*** is any drug that has not been sold in Canada for sufficient time, and in sufficient quantity, to establish its safety and effectiveness under use or its recommended conditions for use

Life of a New Drug (1)

Research

Create/Isolate Chemicals
(14 000 tested to get one as marketable)
(the average cost to develop a new medicine is 1.3 billion)

Tissue/Culture small animals

More specific animal testing and in vitro test (eg: carcinogenicity, reproductive studies…)

Human Testing (Clinical Trial)

Special Access Programme (SAP) (emergency release)

HC approval required

All testing is done, drug company completes analysis of data, prepares a New Drug Submission (NDS)

Health Canada Review/Decision

Post Market Surveillance

Provincial Formulary Decisions

CCOHTA - CDR (only for NDS)

PMPRB (Price Controls)

Life of a New Drug (2)

Industry

Create/Isolate Chemicals
Tissue/Culture
More Specific Animal Tests

Human Testing (Clinical Trials)

Prepare New Drug Submission
Common Drug Review (CDR)

Negotiate with Provinces
Marketing and Promotion to Physicians

Updates to Product Monographs
Dear Health Care Provider Letters Actions
Product on Market or Removal

Government

←HC Approval required
←SAP
←HC Review/Decision
←CADTH
←PMPRB Federal Price Control
←P/T Formulary Decisions
←Post-Market Surveillance

←Post-Market Regulatory actions

Topics to be addressed

- Structure of Health Canada (organizational)
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- **The New Drug Submission (NDS) content**
- NDS review consideration
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New Drug Submission (NDS)

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1. Description of the new drug and its proper name and brand name
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4. **Substantial evidence of the clinical effectiveness**
5. Draft of proposed labelling, including the Product Monograph

NDS (Continued)

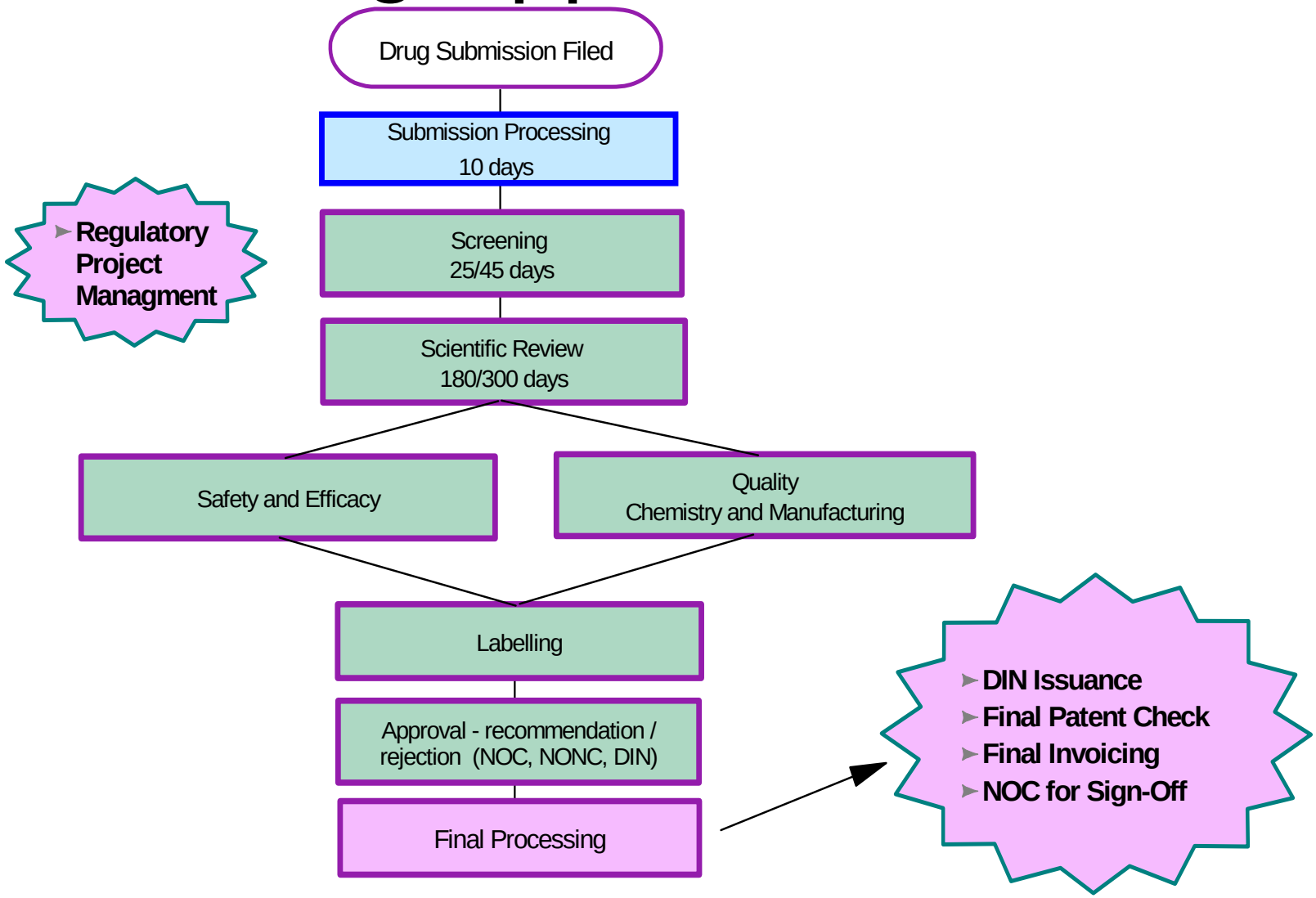
- A New Drug Submission shall include:

4. Substantial evidence of the clinical effectiveness

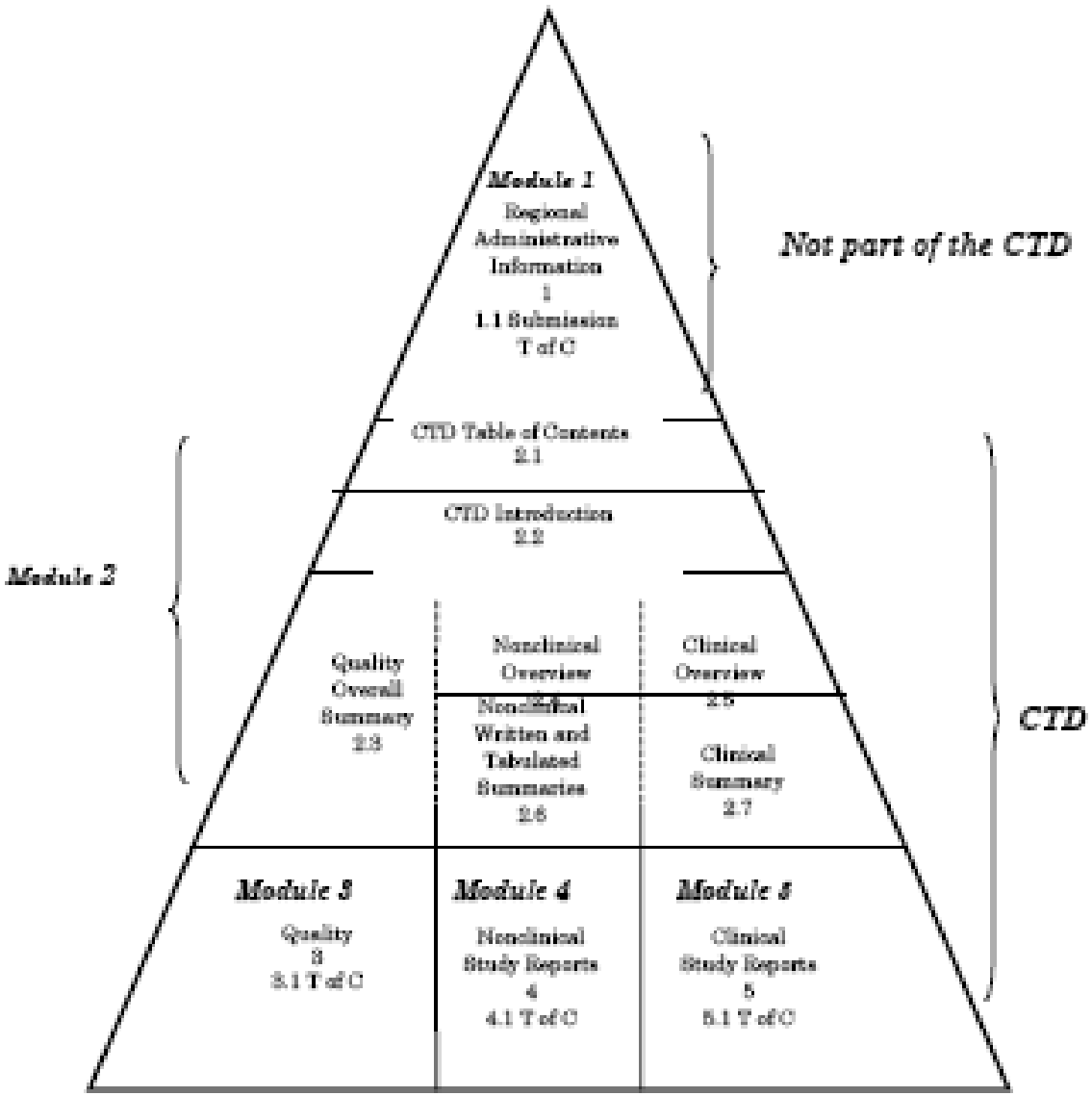
This gives Health Canada the authority to require manufacturers to submit adequate clinical studies, but

This also requires that Health Canada not approve a drug for which substantial evidence of clinical effectiveness has not been submitted

New Drug Approval Process



Diagrammatic Representation of the Organization of the ICH CTD
Common Technical Document



Data for one submission

Pre-Clinical (non-clinical) studies

- Toxicology
- Pharmacokinetics
- Pharmacodynamics
- Microbiology (in vitro and in vivo)
- Relevant non-clinical literature

Clinical studies

- Phase I (human Pharmacology)
  - Pharmacodynamic studies
    - QT prolongation
  - Pharmacokinetic studies
    - Single &multiple dose, children, elderly, renal/hepatic insufficiency, food/drug interaction, subpopulation
- Phase II (Therapeutic Exploratory studies)
- Phase II (Therapeutic Confirmatory studies)
- Clinical Literature

Raw Data

- Composed of case records from the clinical studies for patients who died or had serious and/or severe adverse reactions

Product Monograph (PM)

- The Product Monograph is a factual, scientific document on the drug product; devoid of promotional material; that describes the properties, claims, indications and conditions of use of the drug; and that contains any other information that may be required for optimal, safe and effective use of the drug

New Product Monograph

New Format for Product Monograph

- Part I : Health Professional Information
- Part II: Scientific Information
- Part III: Consumer Information
  - (a lay language translation of the relevant information in Part I and Part II)

PM (contd)

- Part I : Health Professional Information
  - (contains information required for the safe and appropriate prescribing, dispensing and administration of the drug)
- Part II: Scientific Information
  - (contains information similar to the last part of the current PM but with the addition of details of the pivotal trials used to support the approved indications)

Risk / Benefit Assessment (1)

- Do the data support: the drug's
  - Efficacy: Indications, Dosage schedule in adults and special populations
    - The extent to which a treatment achieves its intended purpose and produces a beneficial result
  - Safety: Contraindications, Warnings, Precautions, Adverse Reactions, Overdose
  - Quality: Stability, Impurities, Performance characteristics, Sterility

Topics to be addressed

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AIM OF THE REVIEW

What to do:

Review the pre-clinical and clinical data

- To evaluate whether the data support the claims (indications, dosages, precautions)
- To access the safety and efficacy of the new drug
- To determine whether the risk/benefit ratio of the new drug is acceptable
- To ensure the accuracy of the PM

Aim of the Review (Cont'd)

What not to do:

Do not assume that the new drug has a particular spectrum of anti-microbial activity or is safe and effective because it belongs to an established class of a drug (e.g. macrolide, fluoroquinolones, beta-lactams, etc)

Pre-clinical Studies

- Microbiology
- In vitro studies:
  - Determine the spectrum of activity of the drug against clinical isolates (including those from the clinical efficacy studies
  - Determine the mechanism of action
  - Evaluate the potential for the development of resistance
  - Develop susceptibility testing criteria
- In vivo studies:
  - Animal models for studying effectiveness in infections

Pre-clinical Studies

Pharmacokinetic studies

- Absorption
- Tissue Distribution
- Protein Binding
- Metabolism
- Excretion
- Relationship between blood/tissue levels of drug

Pre-clinical Studies

Pharmacodynamic studies

- Primary pharmacodynamic studies
  - Not relevant for an anti-infective since the site of action is the pathogen and not the host animal
- Secondary pharmacodynamic studies
  - For an anti-infective this would be considered to be an adverse event
  - Interaction with and metabolization by the cytochrome P450 enzymes
  - Cardiac safety testing, in vitro and in vivo
  - Drug-drug interaction studies

Pre-clinical Studies

- Single dose
- Multiple dose
- Reproductive studies
- Mutagenicity, carcinogenecity and photo-carcinogenicity
- Special studies (e.g. irritation, phototoxicity, etc)

Pre-clinical Studies (cont'd)

- Clinical Relevance of the pre-clinical studies:
  - Finding from the phamacokinetics, pharmacodynamic and toxicology studies should be extrapolated to assess the drug's potential safety in humans. Any adverse effects observed in animal studies serve as flags with respect to safety evaluation in the human trials. In addition, carcinogenicity and the reproductive toxicology studies are of particular importance since such studies cannot be carried out in clinical trials. Such information is only obtainable through post-marketing epidemiological studies.

Clinical studies

Phase I – First/Early exposure in Humans

- Pharmacokinetic and pharmacodynamic studies
- Trials of limited size to get a “hint” of efficacy
- Most frequent adverse drug reactions may be observed

Phase II – Explore/Establish Efficacy

- Larger efficacy trials, normally beginning with the less serious indications
- Starting to generate a larger safety data base

Clinical studies

Pharmacokinetic studies

- A, D, M, E
- Pk's at steady state
- Pk's in subpopulations, children, elderly, women, renal and hepatic impaired function, diseased states such as cystic fibrosis, etc)
- Pk's fasting and fed state for oral drug
- Drug-Drug interaction studies

Clinical studies

- Pharmacodynamic studies
  - Primary pharmacodynamics (in case of antibiotics – the primary information is from in vitro microbiology studies
  - Secondary pharmacodynamics
    - For anti-infectives secondary PD effects can be very important and are menifested as ADRs
    - The areas of greatest concern at this moment are QT interval prolongation. Guidelines are now available for conducting studies to adequately determine this potential.

Clinical studies

Phase III: confirm and extend efficacy studies to various indications

- Pivotal Studies:
  - The indications for a drug are based on the results of these studies
  - These studies are normally comparative and against a drug (marketed in Canada) which has the same indication as that being studied
- Non Pivotal studies:
  - These are generally not sufficiently robust or well designed to be useful for demonstrating efficacy. They do, however, contribute to the safety data base

Clinical studies

- Pivotal studies
  - The design of these studies is normally based on guidelines such as those published by infectious diseases societies, by the FDA (points to consider)
  - Studies are required for each indication
  - In general, two studies are required for each of the intended indication
  - The studies are evaluated for both microbiologic and clinical response at the end of treatment and at various selected times after the end of the treatment

Clinical studies

- Pivotal studies
  - Claims are granted by Indication and by pathogen identified in those patients enrolled for specific indication
  - The recommended dose and duration of dosing is specific for each indication and is based on what was studied in the clinical trial for that indication
  - Safety is assessed on the combined total of all the patients administered the study drug and is assessed for each of the doses and duration of dosing

Clinical studies

- Pivotal studies
  - The risk analysis and the Contraindications, Warning and Precautions of the PM are based on the pre-clinical studies, the safety data from the clinical studies and the known class effect
  - Special Efficacy/safety studies
    - Special population such as children, the elderly and women
    - Further study of class effects (QT – fluoroquinolones)

Types of New Drug Reviews

- Normal Submission (NDS)
  - Data requirement as outlined
  - Performance standard is 300 days
- Notice of Compliance with Conditions (NOC/c)
  - Serious, life-threatening or severely debilitating diseases or conditions; earlier access to new drugs based on “promising evidence” of clinical benefit providing it possesses an acceptable safety profile
  - The manufacturer must agree to carry out confirmatory Phase IV studies to verify the clinical benefit of the drug and further establish the safety profile
  - Performance standard is 200 days

Types of New Drug Reviews

- Priority Review
  - Provide earlier access to a drug for which there is substantial clinical evidence that the drug provides effective treatment for a disease for which no drug is presently marketed in Canada or
  - There is a significant increase in efficacy and/significant decrease in risk such that the overall risk/benefit profile is improved over existing therapies
  - Performance standard is 180 days

Performance Target - Example

- Performance Target for a NAS
  - 10 days processing
  - 45 days screening 1
  - 300 days review 1
  - response to NON
    - 45 days screening 2
    - 150 days review 2

355 days = Time to First Decision

550 days if a NON is issued

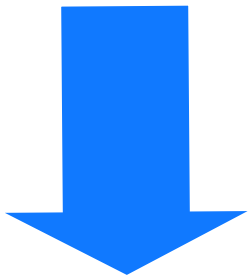
- Performance Target for a Priority NAS
  - 10 days processing
  - 25 days screening 1
  - 180 days review 1
  - response to NON
    - 25 day screening 2
    - 90 days review 2

215 days = Time to First Decision

330 days if a NON is issued

Risk Benefit Assessment

Information from
Pre-clinical and clinical
trials



Potential Risk Vs
Anticipated Efficacy

Efficacy
Adverse Reactions
vital signs, ECG
lab abnormalities

Product Monograph

Indications
Contraindications
Warning
Precautions
ADR
dosage

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Anti-Infective Drugs

- Some trends
  - Development of new antibiotics is declining over last several years
  - Extension of existing indications
  - Shorter duration of treatment
  - Initial application for one or two indications often cSSTI (complicated Skin and Soft Tissue Infections)
  - Study of more resistant pathogens

Indication Section

- Evolution of wording used for indication
- Respiratory tract infection – CAP, HAP, VAP etc
- Clearly defined – often indicated by what is studies in trials ex. cSSTI including diabetic foot infection
- Listing of pathogen – Adequate number of monomicrobial pathogens (40-50) less if unusual pathogens
- Only known and recognized pathogens – MRSA or VREF

Supporting data

- Issue of Non-Inferiority trials
  - Appropriate use of comparator (product approved in Canada); used at appropriate dose and duration for a defined indication
- Acceptable – issues have been raised for certain indications – ABECB; sinusitis, Acute Otitis Media
- Non-Inferiority Margin – defined

Product Monograph Issues

- Old vs New PM format – important differences for antibiotic PMs
  - Conversion is not easy as some sections of New PM format were not populated for antibiotics – clinical trials section
  - Comparators (different for different indications) – often many and therefore presentation is difficult to interpret
  - Tabular format – Design and micro/clinical cure rates
  - Data for approved pathogens only (exception ?)

Interaction with the Division

- Regulatory Project Manager – issues related to all anti-infective drug submissions
- Scientific issue – reviewers
- Pre-NDS meeting
- Teleconference, face to face, clarifaxes
- Provide information on interactions with other regulatory agencies


COLA

Goal

- To ensure that the antibiotics that are approved for use in Canada meet the standard for quality, safety and efficacy.

Thank you

- Thanks to the members of the Division of Anti-Infective Drugs