Regulación de Productos Biotecnológicos en Canada

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Outline

- Regulation of Biologics / Biotechnology Products in Canada
- Fundamental issues with biotechnology products
- Biosimilars / subsequent entry biologics

Terminolgy

- Biological medicines
- Biologicals
- Biologics (North America)
- **Biotechnology Products**

- Used in prophylaxis, therapy or diagnosis of human diseases (in vitro diagnostics)

Regulation of medicinal products in Canada

- The Federal Government regulates the quality, safety and efficacy of medicinal products under the **Food and Drugs Act**
- Covers both **clinical trials** and **market approval** (licensing)
- The regulator is **Health Canada**

Legal Framework- Canada

- **Food and Drugs Act**
- Act defines 4 types of products

-Drug

-Food

-Device

-Cosmetic

- Term “drug” further defined through separate schedules to Act –**Schedule D covers biologics**

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Legal Framework- Canada

- **Food and Drug Regulations** (details)

  General Requirements

  Establishment Licensing

  Good Manufacturing Practice (Biologics)

  Schedule D - Biologic Drugs

  Clinical Trial Applications

  New Drugs / generics

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Documentation

- Health Canada own Regulations and guidelines eg Risk Based Lot Release
- Regulations refer to USP / European Pharmacopoeia (No Canadian)
- Adopt ICH guidance (biotherapeutics)
- Refer to WHO Recommendations for vaccines (future may refer in Regulations)

The Food and Drugs Act

- The Act provides Health Canada with broad powers to prevent the distribution of any biologic which:
  - has been manufactured or stored under “unsanitary” conditions
  - has been adulterated, labelled, sold or advertised in a misleading/deceptive way
  - has been manufactured on premises and/or under conditions which have not been approved by the Minister of Health
- The Act also provides Health Canada with the authority to designate inspectors who can:
  - enter facilities at any reasonable time to examine records and articles
  - open and examine packages
  - make copies of records and take samples
- The Act also provides for the authority to make regulations under the Act
- The Act also provides the Minister with the authority to make interim regulations in the event of a public health emergency

Regulations apply to all

- No special regulations for imported products – all treated same way
- Many products from global producers
- Some Canadian produced biological products
- Vaccines – Two global producers in Canada , Sanofi Pasteur (Toronto), GSK (Montreal / Quebec City for seasonal and pandemic influenza vaccines gobal supply) : Canlab also small producer.

Health Products and Food Branch – Regulatory arm of Health Canada

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

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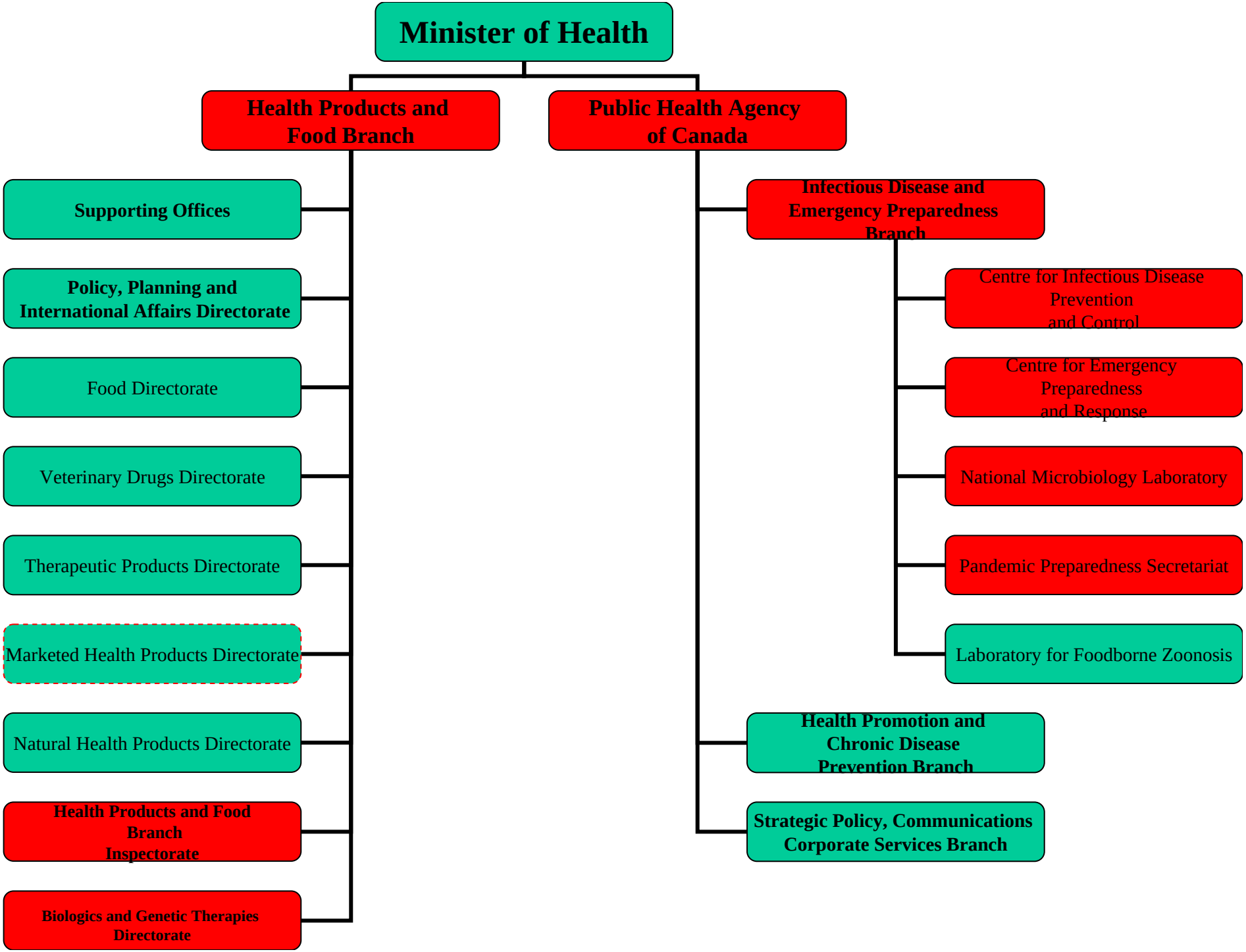

Minister of Health
Health Products and Food Branch
Public Health Agency of Canada
Supporting Offices
Policy, Planning and International Affairs Directorate
Food Directorate
Veterinary Drugs Directorate
Therapeutic Products Directorate
Marketed Health Products Directorate
Natural Health Products Directorate
Health Products and Food Branch Inspectorate
Biologics and Genetic Therapies Directorate
Infectious Disease and Emergency Preparedness Branch
Centre for Infectious Disease Prevention and Control
Centre for Emergency Preparedness and Response
National Microbiology Laboratory
Pandemic Preparedness Secretariat
Laboratory for Foodborne Zoonosis
Health Promotion and Chronic Disease Prevention Branch
Strategic Policy, Communications Corporate Services Branch

Regulation of medicinal products in Canada

- **Drugs (chemical drugs)** / Medical Devices – responsibility of the Therapeutic Products Directorate

- **Biological medicines (biologics)** – responsibility of the **Biologics and Genetic Therapies Directorate**

Regulation of medicinal products in Canada

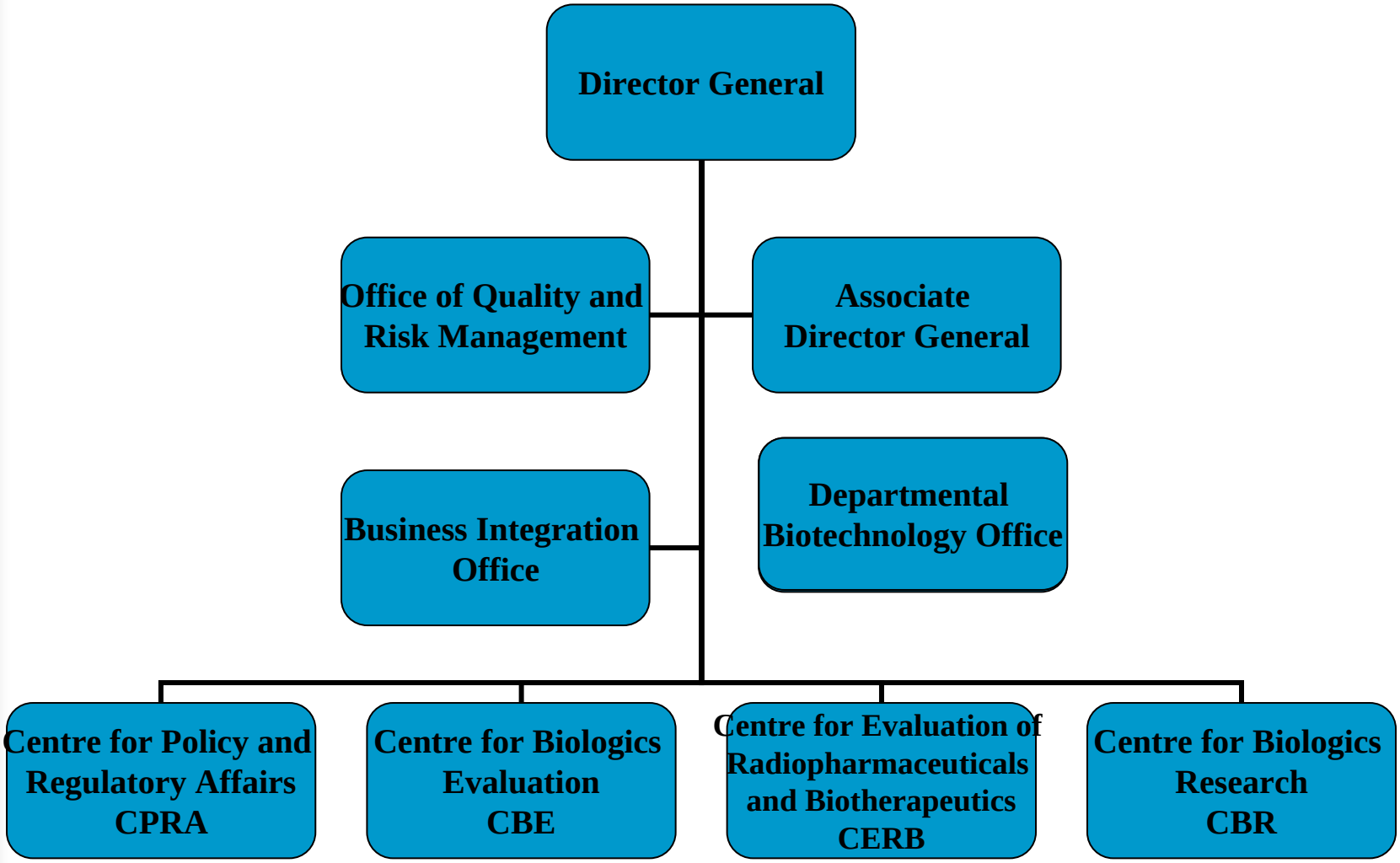
- **Compliance and Enforcement** is undertaken by the Health and Food Products Branch Inspectorate (Member of PIC)

- **Post-marketing surveillance** undertaken by the Marketed Health Products Directorate and, for **vaccines /blood**, Public Health Agency of Canada

Biologics and Genetic Therapies Directorate (BGTD)

- the Canadian federal authority responsible for **the regulation of biological drugs and radiopharmaceuticals** for human use
  - Clinical Trial Review and Authorization
  - Pre-market review and Authorization
    - Includes laboratory testing and on-site evaluation
  - Develops new policies and regulatory framework as needed and keeps existing ones updated
  - Post-approval lot release of vaccines and other biologics

Organizational Structure of BGTD



Biologics and Genetic Therapies Directorate : Organization

Four separate Centres - approx 300 staff

- *Centre for Biologics Evaluation*
- *Centre for Radiopharmaceuticals and Biotherapeutics*
- *Centre for Policy and Regulatory Affairs*
- *Centre for Biologics Research*
- *Departmental Biotechnology Office*
- *Office Director General*

Biologics and Genetic Therapies Directorate : Organization

- ***Centre for Biologics Evaluation -Divisions***

  Vaccines, Blood and Plasma Products

  Cells Tissues and Organs

  Clinical Evaluation

- ***Centre for Radiopharmaceuticals and Biotherapeutics – Divisions***

  Monoclonal antibodies, Cytokines , Hormones, Radiopharmaceuticals , Clinical evaluation

Biologics and Genetic Therapies Directorate : Organization

- ***Centre for Policy and Regulatory Affairs***
  Drafts policies / regulatory framework;
  submission management

- ***Centre for Biologics Research***
  Structure-function of biological molecules,
  molecular biology / genetics,
  new assay technologies

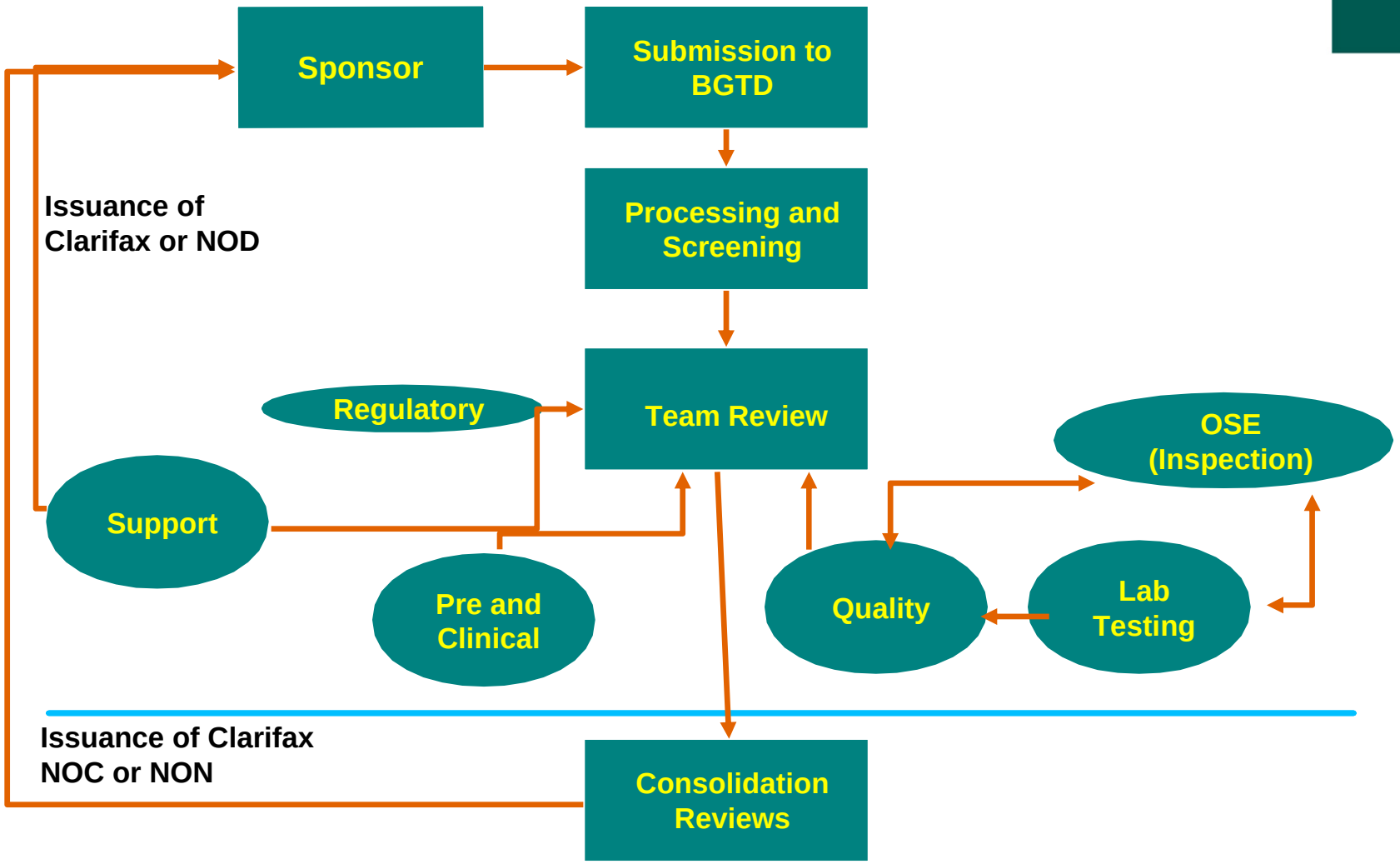
Biologics and Genetic Therapies Directorate : Review Activities

Review applications for clinical trials, for marketing authorization and for changes to licensed products -production / indication

Pre-approval product specific **on-site evaluation** of manufacturers/production processes (different from GMP inspection)

Pre- and post - approval laboratory evaluation (lot release of vaccines, blood products)

Submission Review Process



Review Outcomes

- Notice of Compliance (authorization)
- Notice of Compliance with conditions
- Notice of Deficiency (not enough data to make a decision)
- Notice of Non Compliance (disagree with interpretation of data)
- Applies to Canadian products and imported – no difference

New Developments

- Summary Basis of Decisions posted on Health Canada website (positive NoC)
- Propose Future to post summary basis for rejection (Non compliance or deficiency)
- Monograph now posted on website (English . Soon French)
- Food and Drug Act under revision – Progressive Licensing- to strengthen Act

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Recent Developments: Memorandum of Understanding

- FDA
- EMEA
- TGA (Australia)
- SwissMedic
- Singapore
- Learning to work under agreements- TGA (parallel reviews): FDA (prelicensing discussions)

Why this regulatory attention to biologics and biotechnology products?

WHAT IS THE PROBLEM ?

Why are these products not simply like chemical drugs?

Terminolgy

- Biological medicines
- Biologicals
- Biologics (North America)
- Biotechnology Products

In Canada biologics and **biotechnology derived** medicines under same umbrella – **all biologics**

Regulation of biological medicinal products in Canada

- Vaccines
- Plasma derivatives and labile blood products (including blood collection centres)
- Cells , tissues and organs
- Biotherapeutics – rDNA derived biologics, monoclonal antibodies, gene transfer products and traditional products isolated from biological materials (enzymes, hormones etc)

Other jurisdictions

- European Union the Directives define biotechnology and high technology medicinal products
- These products undergo regulatory review through the Centralized EMEA procedure
- US FDA biologics, including biotechnology products, regulated under Public Health Act (not Food and Drug Act)

Biologics / Biotechnology Products: What's the Problem?

- **Differ from Chemical Drugs in number of ways**
- **Biologicals** present particular problems with respect to quality, safety and efficacy
- **Highly complex** in molecular terms and cannot be **fully characterized** by physico-chemical means **alone**
- Sometimes defined in national legislation – vaccines, immunologicals, hormones, blood products , cells , tissues , organs.

BIOLOGICALS

- UK -- “substances used in medicine whose purity or potency cannot, in the opinion of the Secretary of State, be adequately assured by physical or chemical means” (Biological Standards Act 1975)
- **Distinguishes chemical drugs**
- WHO – 3 features: biological starting materials: biological production process: need for biological test method for potency /purity (safety) (WHO 1990)

Biologics / Biotechnology Products: What's the Problem?

- Biological starting materials and /or manufacturing process - **inherently variable by nature**
- Some products consist of live attenuated organisms (vaccines, genetic therapy products)
- Test methods needed to characterize product are biological in nature (bioassays) – potency (activity), immunogenicity, safety

Biologics / Biotechnology Products: What's the Problem?

- Deleterious effects of drugs usually based on their chemical nature
- Major problems /accidents with biologicals often **batch related**

Major problems with biologics often batch related

- Cutter incidence (1955)-failure to completely inactivate polio vaccine
- Transmission of CJD by pituitary growth hormone / dura mater
- Contamination of blood products by hep C virus or HIV / failure to completely inactivate viral contaminants

Safety of Biologicals

- **Problem may not be restricted to recipient**
- A contaminating virus in a vaccine/blood product/tissue MIGHT spread to contacts
- Could become serious threat to health of a country or globally – no borders for bugs
- SV40 & attenuated polio vaccine (OPV)

Continued Vigilance Essential

Ensuring Consistency of Production

- Consistency of production of paramount importance
- Long term - drift
- Product does not differ from lots shown safe and effective in clinical trials
- **Production changes could lead to major adverse effects**

Biologics production - In process controls

Standardization and quality control of the **PRODUCTION PROCESS** as important as tests on final product

“Belts and braces” approach

(braces = USA suspenders)

Redundancy as in aircraft design

Biologics production - In process controls

- Need to understand origin of materials (production cells, seeds)
- Tests on starting materials
- Tests on intermediates
- Tests on final product
- Independent Lot Release by regulator

Biotechnology derived medicines

- Are all these controls needed ?
- Are these not well characterized compared with the traditional biologicals (vaccines)?
- Answer , yes, but they still have same problems as traditional biologics

Biotechnology Derived Products

- Past 25 years seen explosion in molecular biology/novel bioproduction methods
- Opened new possibilities for disease diagnosis/treatment /prevention
- Cutting - edge of biomedical research
- Economically fastest growing sector in pharmaceuticals

Quantum jump

- Sequencing nucleic acids
- Ability to “word process” - **“cut, copy, alter, paste” DNA sequences from genes**
- **Express genes in foreign cells -** transfer text to new disk and print
- Ability to purify and to **characterize biological macromolecules in great detail**

Biotechnology Derived Products

- Range rDNA derived proteins (novel & replacements) (cells/**animals/plants**)
- New molecular based medicines- gene therapy/ DNA vaccines
- New diagnostic measures – gene amplification technology for viral safety testing of blood (HIV/ West Nile Virus)
- Learning to manipulate cells, tissues, organs, xenotransplants

Regulatory oversight of novel biotechnologies

- Appropriate regulatory measures essential to **minimize the risks & maximize benefits**
- **to safeguard patients and populations against unacceptable adverse events and ineffective products**
- **to ensure that they are given full benefits of scientific innovation and knowledge**
- **to ensure the reliability of diagnostics**

REGULATORY APPROACH TO PRODUCTS OF NOVEL BIOTECHNOLOGIES

CHALLENGE

- *TO ENSURE PUBLIC SAFETY*
- *NOT TO INHIBIT DEVELOPMENT*

Regulatory oversight

- **REGULATORY MEASURES** put in place **very early on** in development of biotechnology products - **regulated as biologics** (Canada, Europe, USA)
- **GUIDELINES** on production and quality control rDNA derived proteins **also available from early days** (EMEA, FDA, ICH, WHO)
- Provide framework for moving forward with newer technologies

Guidelines

- Based on sound science
- **Flexible approach**
- Recommendations could be updated in light of experience of production and use and with further development of new technologies.

Traditional Biologics vs Biotechnology Products

- Historically, regulatory requirements for production, characterization and quality control of traditional biologics followed some **“problem”** relating to safety or efficacy
- **Contaminated polio vaccine; transmission HIV/Hep C by blood products : CJD and pituitary growth hormone**
- Biotech products guidelines developed in attempt to **prevent** problems arising

Product characterization-key

- Means **more** than simple quality control tests
- Expect **several** parameters to be evaluated by different techniques, not just one
- Protein sequence, secondary / tertiary aspects, glycosylation, phosphorylation, oxidation, lipidation, etc
- Product / **host** related impurities (quantity, identification)
- Formulation implications and Stability

Biotechnology derived products

- Led to “well characterized biologics”
- Best characterized and controlled biological products on the market
- Extremely safe and effective medicines
- But still control procedures in place cannot **FULLY** predict biological properties and clinical performance

A word of Caution

- **Expect the Unexpected**
- rDNA derived insulin first licensed in UK early 1980s
- Quality controls proposed by manufacturer lacked suitable in process controls
- RELUCTANTLY manufacturer agreed to include end of fermentation assay for plasmid characterization – interesting outcome

  (plasmid gene for insulin in E coli)

Expect the Unexpected

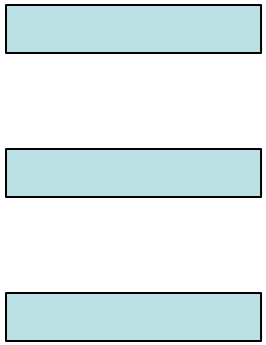
- Quality control of the product involved examining plasmid by sizing
- Over 400 very large scale fermentations carried out successfully over 12- 18 months
- UK regulator about to relax control and declare system stable
- Surprise

Expect the Unexpected

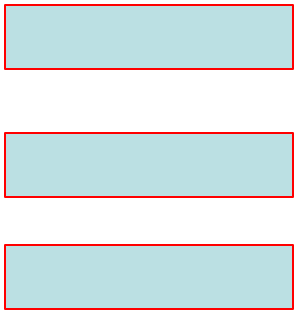
- Surprise very poor product yield (20 – 30% normal) in one large fermentation
- All other parameters normal, bacterial growth, fermentation characteristics (temperature, oxygenation)
- The quality control measure enabled rapid resolution of the problem

Plasmid sizing on electrophoresis gel

Separating DNAs and checking their size



routine



unexpected

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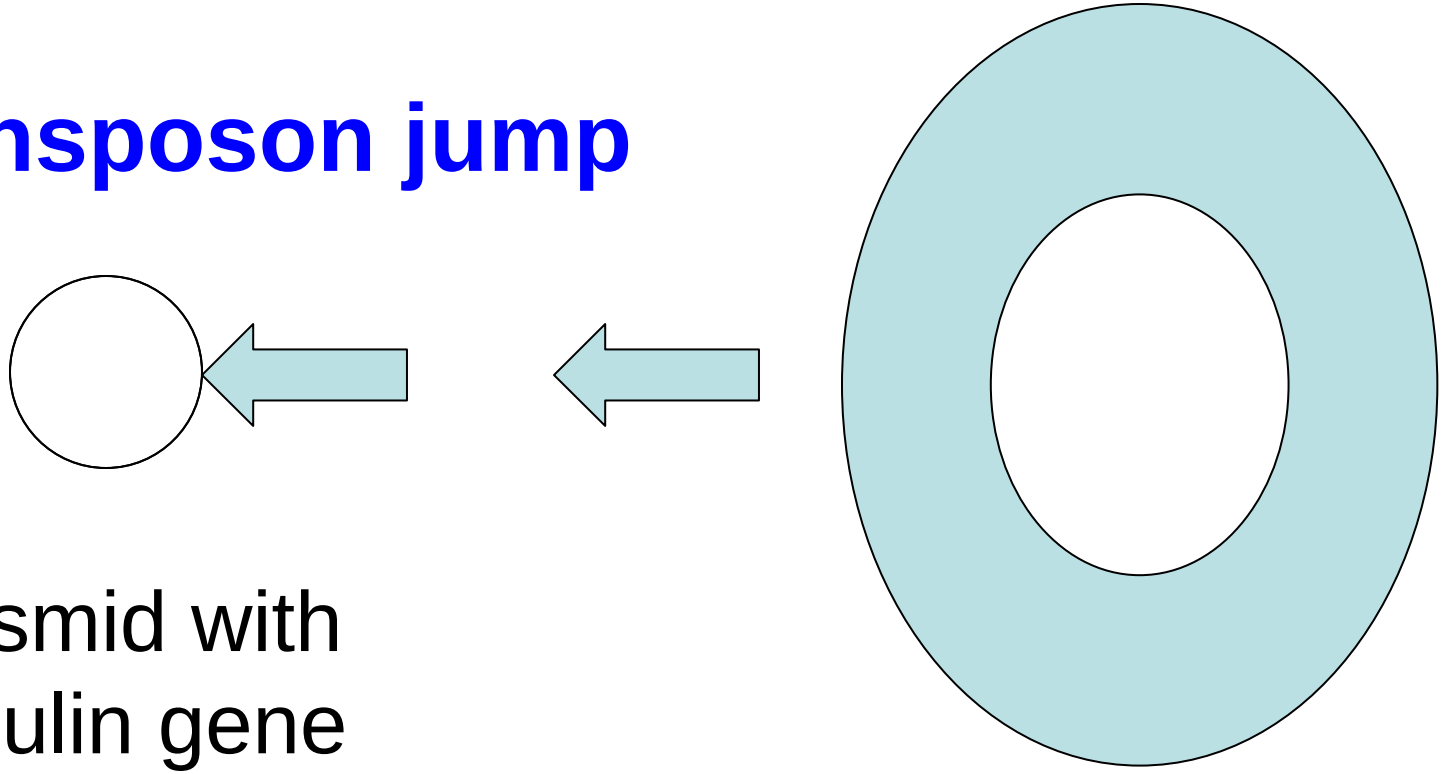
•Jumping Genes

transposon jump



plasmid with
insulin gene

chromosome

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Expect the Unexpected

- Transposon inserted into operator of the insulin gene shutting down expression
- System had been biologically stable for long time
- Led to manufacturers screening production strains of *E coli* for transposable elements and deletion
- Only transposon free strains used

Genetic Stability and Product Consistency

- Concern in early 1990s that low level variant DNA sequences in the production gene would lead to variant proteins in the product which might go unnoticed
- Insensitivity of protein characterization
- That the variant proteins might be detrimental by binding to receptors or have unwanted biological properties (immunogenic)

Control Points

- Cell bank / bacterial host
- **Sequence of transfected gene**
- Cell culture / fermentation
- Separation and purification
- Bulk product testing
- **Characterization resulting protein**
- Final product testing

Genetic Stability and Product Consistency

- Concern that transfected gene sequence gave only consensus DNA sequence
- Variants might be missed
- Proposal made to clone the transfected gene many times and sequence each individual clone to arrive at a statistically sound estimate of variant sequences
- If variant 10%, necessary to sequence 28 clones to detect with 95% confidence

Genetic Stability and Product Consistency

Value of multiple sequencing questioned – does not guarantee absence of variants

- Possible mutational events during fermentation
- Transcriptional errors
- **Translational errors**
- Protein processing effects

Translational errors during rDNA protein synthesis

- Known to occur at low level in prokaryotic systems like *E coli*
- Expressing foreign proteins at high rates to make them major cell components can lead to increased frequency of error rates in production cells -nutritional stress
- Error rates in E coli about 0.1%. It is 25 times greater during high level synthesis of mouse epidermal growth factor

Translational errors during rDNA protein synthesis

- High level synthesis of Somatropin and interleukin 2 in E coli gives rise to errors
- Both have high levels of leucine and over-expression creates unusually high demand for leucine
- E coli responds by increasing biosynthesis of leucine and an intermediate- norleucine- accumulates
- Norleucine is structural analogue of methionine and gets incorporated into the protein instead of methionine

Translational errors during rDNA protein synthesis

- Resolved by supplying high levels of leucine during fermentation
- Problems of translational and other errors need to be detected at the product characterization level
- In recent years technology for protein purification and characterization has improved considerably

Analytical Advances

- Can thoroughly characterize product with respect to key criteria
- Mass, primary structure (amino acid sequence), secondary and tertiary structures, post- translational changes
- Biological activity - behaviour in bioassays
- International reference materials available in some cases from WHO or European Pharmacopoeia

Analysis of complex glycoproteins

- **Combination** of analytical methods
- Amino acid backbone - HPLC, electrophoresis, peptide mapping, mass spectrometry, enzymic cleavage
- Glycosylation - quantitative composition, monsaccharides, glycan mapping (HPLC), structural characterization, site occupancy

Biotechnology derived products

- Product issues
- **Process issues - residual host cell proteins, residual DNA from continuous cell lines, viral safety**

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Biotechnology derived products

- Residual host cell DNA from transformed (continuous) cell lines
- Concern - transfer of oncogenic DNA to recipients
- WHO recommendations as to allowable levels of DNA

Viral safety of biotechnology products - critical

- Measures needed to ensure absence of infectious agents in product
- Cell banks and production cell banks must be carefully screened
- Validation of virus removal / clearance

Biotechnology Products- dealing with regulatory details

* Development genetics
* Cultivation and harvesting
* Downstream processing
* Viral validation studies
* Testing and release
* Pre-clinical studies/toxicology
* Clinical studies/several lots to be used

Biotechnology Products- dealing with regulatory details

- Traceability of source materials – Bovine/human materials as excipients or in production**.(TSE issues)**
- **Scale up** (from phase I/II to III) – comparability issues – **major issue**
- Viral safety and clearance issues – How much and at what stage of clinical study? As much as is reasonable – risks/benefits at different stages (phases I/II/III, recipient types) will vary . **Don't underestimate viral contamination issues!!**

Biotechnology Products- dealing with regulatory details

Other issues to tackle

- **Immunogenicity of rDNA derived product -** major issue
- **Potency assay -** need for regulatory authority to check out assay . Often source of difficulty . Standardization issues
- **Setting specifications –** need to be based on real data

Biotechnology products

- Development and manufacturing complex
- Very sensitive to production parameters
- Nature of cell substrate and growth conditions / downstream processing
- Minor changes can have major effects on biological activity
- **Key issue potential immunogenicity**

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Potential immunogenicity- product safety

- Most biologicals induce some antibodies
- Foreign proteins (streptokinase) induce antibodies via classical vaccine-type reaction
- Human homologue proteins(interferon, cytokines) induce antibodies by breaking B-cell tolerance
- Various factors involved- impurities and aggregates considered to be major cause
- Single or multiple dose also a consideration

Potential immunogenicity - key event 2002

- Pure red cell aplasia related to use of Erythropoetin (epoetin) – a major event
- In 2002 , 13 cases noted all associated with epoetin treatment – Antibodies to epoetin
- Product Eprex had been safely used for many years.
- Factors thought involved formation of micelles associated with epoetin, silicon droplets in prefilled syringes
- **Major changes in formulation**

Potential immunogenicity

- Such adverse events cannot be predicted
- Need for vigilance especially after manufacturing changes

Manufacturing Changes - Risks

- **Change filter – Risk low** – analytical data, process studies
- **Move to new facility – Risk moderate-** process studies, stability studies
- **New cell line / major formulation change- Risk High-** analytical data, stability studies, clinical evaluation

REGULATORY CHALLENGES OF NOVEL BIOLOGICS

- Novel systems = novel scientific/technical issues – eg plant derived products
- Recognizing and adequately dealing with scientific/technical problems early in development of product / technique
- Ensure sound scientific data base available on which to make regulatory decisions
- Ensure regulatory position adequately reflects scientific advances - **international dimension**

Why this regulatory attention to biologics and biotechnology products?

- See that biologicals /biotechnology products need very special attention
- More complex regulatory oversight than chemical drugs.

New challenges in Regulation of Biotechnology Products

- Biosimilar products
- Subsequent entry biologics

Biotechnology Derived Medicines

- Increasing number of patents/data protection for biological medicinal products expiring in coming years – some already expired
- Recently newer products appearing on the horizon – Biosimilars / Subsequent Entry Biologicals
- This has led to a flurry of activity both with manufacturers and regulatory authorities worldwide – **how to handle the regulation of these products**