Biologics are "Different":
The Regulation of Biological Drugs in Canada

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Presentation Outline

- A brief history
- Approach to biologics regulation
- Regulatory challenges
- Conclusions

"The past, the infinite greatness of the past!
For what is the present after all, but a growth
out of the past?"

Walt Whitman, *Passage to India*

Evolution of regulatory authority for Drugs in Canada - 1875 to 1919

- "The Inland Revenue Act of 1875" - A law to prevent manufacture and sale of adulterated food, drink and drugs

- "The Adulteration Act of 1884"
  - 1st legislation of its kind in North America
  - official standards for drug composition
    - meet British or US Pharmacopeia or other recognized standard
    - strength/purity to meet professed standard (as offered for sale)
  - 1890 Amendment - allowed standards set by "Orders in Council"

- "Proprietary or Patent Medicines Act", 1909
  - registration of secret-formula packaged medicines for internal use
  - 1919 Amendment - gave control over advertising & prohibited claims of a cure for any disease

Evolution of regulatory authority for drugs in Canada - 1920 to 1952

- "An Act Respecting Food and Drugs" - 1920
  - ► administered by new Department of Health
  - ► concept of 'delegated legislation' for enacting regulations
  - ► concept of "misbranding" (borrowed from US 1906 Act)
  - ► Schedule B listing "serums" and other biological substances
  - ► 1927 Amendment
    - • authority to license manufacturers of certain scheduled drugs, including endocrine preparations, serums, toxins, vaccines and analogous biological preparations
    - • authority to cancel/suspend a licence for violation of regulations
    - • requirement to submit test samples of each lot
  - ► 1941 Amendment
    - • certain drugs only available via individual prescriptions
  - ► 1951 Amendment
    - • need NDS prior to marketing to support safety; leads to NOC
    - • notification of clinical trials

Evolution of regulatory authority for drugs in Canada - since 1953

- "The Food and Drugs Act" - 1953 (current authority)
  - ► major reorganization of old Act (Schedule B becomes Schedule D, etc.)
  - ► prohibition of the manufacture, preparation, preservation, storage or sale of foods drugs or cosmetics under unsanitary conditions
  - ► 1963 Amendment
    - extensive revisions affecting "new" drugs
    - submissions be filed for clinical trials
    - inspection program for all drug plants
    - NOC for NDS requires substantial evidence of safety & effectiveness
    - authority to suspend a clinical trial or a NOC
  - ► 1973 Amendment
    - issuance of a Drug Identification Number
  - ► 1974 Amendment
    - clinical protocols are reviewed and NOC issued
  - ► many more amendments and operational policies
- After 50 years, legislative renewal is again a priority !

Regulatory Authority for Biologics

- The Food and Drug Act (1920) provided authority for creation of a national laboratory for public health with work including:
  - inspection, examination and certification in reference to medicinal chemicals and biological products
  - investigation into diseases
  - investigation into causes of ill health
- By 1925, the name became "Laboratory of Hygeine" with Bacteriology and Pharmacology Sections
- First animal breeding colony was established in 1931
- In 1944 the Virus Laboratory was established in time to prepare for the vaccine era of the 50's and 60's
- In 1946 the Pharmacology Section was transferred to a new directorate known as "The Food and Drug Divisions."

Regulatory Authority for Biologics

- Between 1946 and 1970, biologics regulation was divided between the Laboratory of Hygeine and The Food and Drug Divisions
- In 1966, the Viral Laboratory became recognized as a WHO Collaborating Laboratory
- In 1970 the Laboratory of Hygeine became the Laboratory Centre for Disease Control (1970)
- In 1972, the Health Protection Branch was created incorporating the LCDC and the Directorates of Food, Drugs and Environmental Health

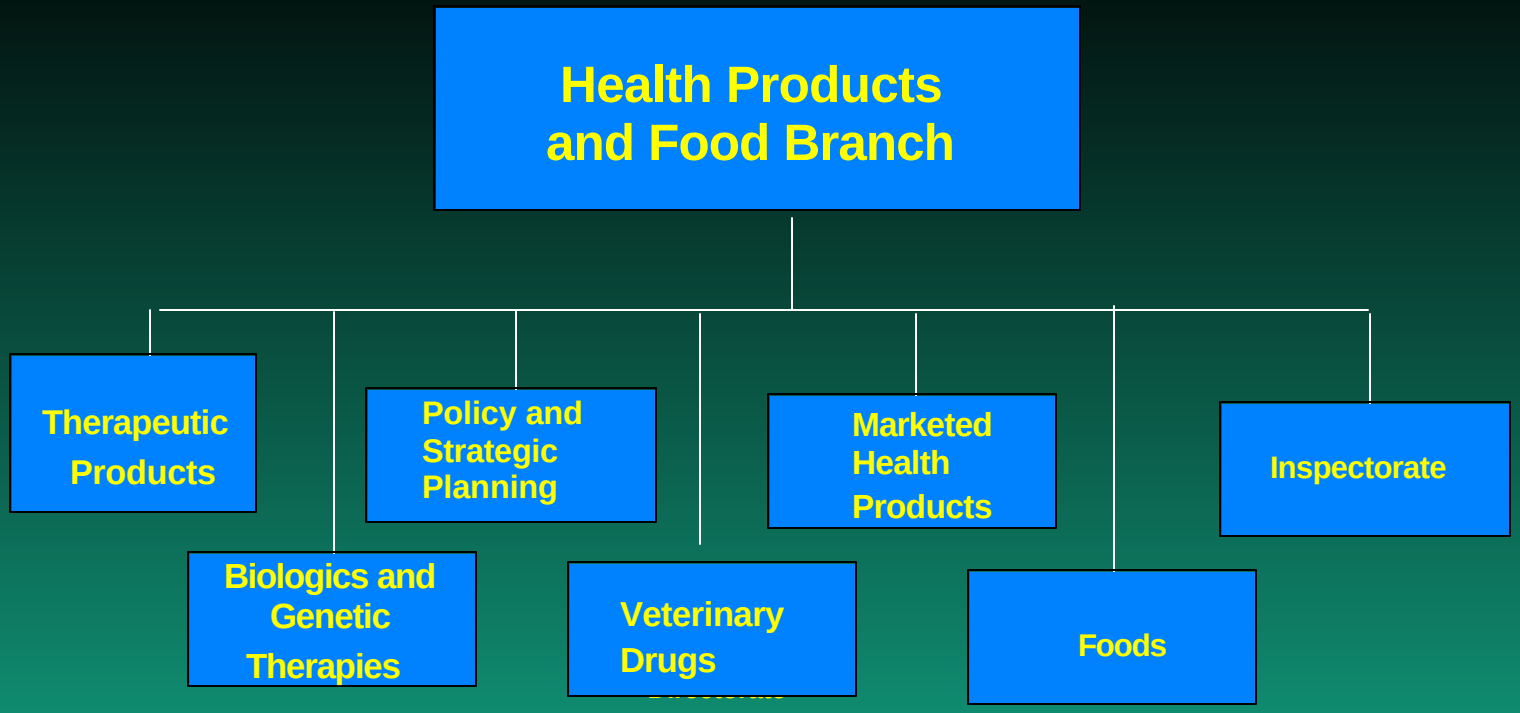
Regulatory Authority for Biologics

- In 1974, the Biologics Control Bureau moved from LCDC to become a separate Bureau within the Drugs Directorate but still providing "support" to the regulatory authority centred in the Bureau of Drugs

- Following a reorganization in 1980, biologics regulation became fully integrated into the Bureau of Biologics (BB) which assumed full authority for biologics (just in time for the first products of rDNA)

- 1995 - Radiopharmaceuticals Division joined BB (BBR)

- 2000 - As part of a major Branch and Directorate reorganization, BBR became a new directorate eventually renamed Biologics and Genetic Therapies Directorate

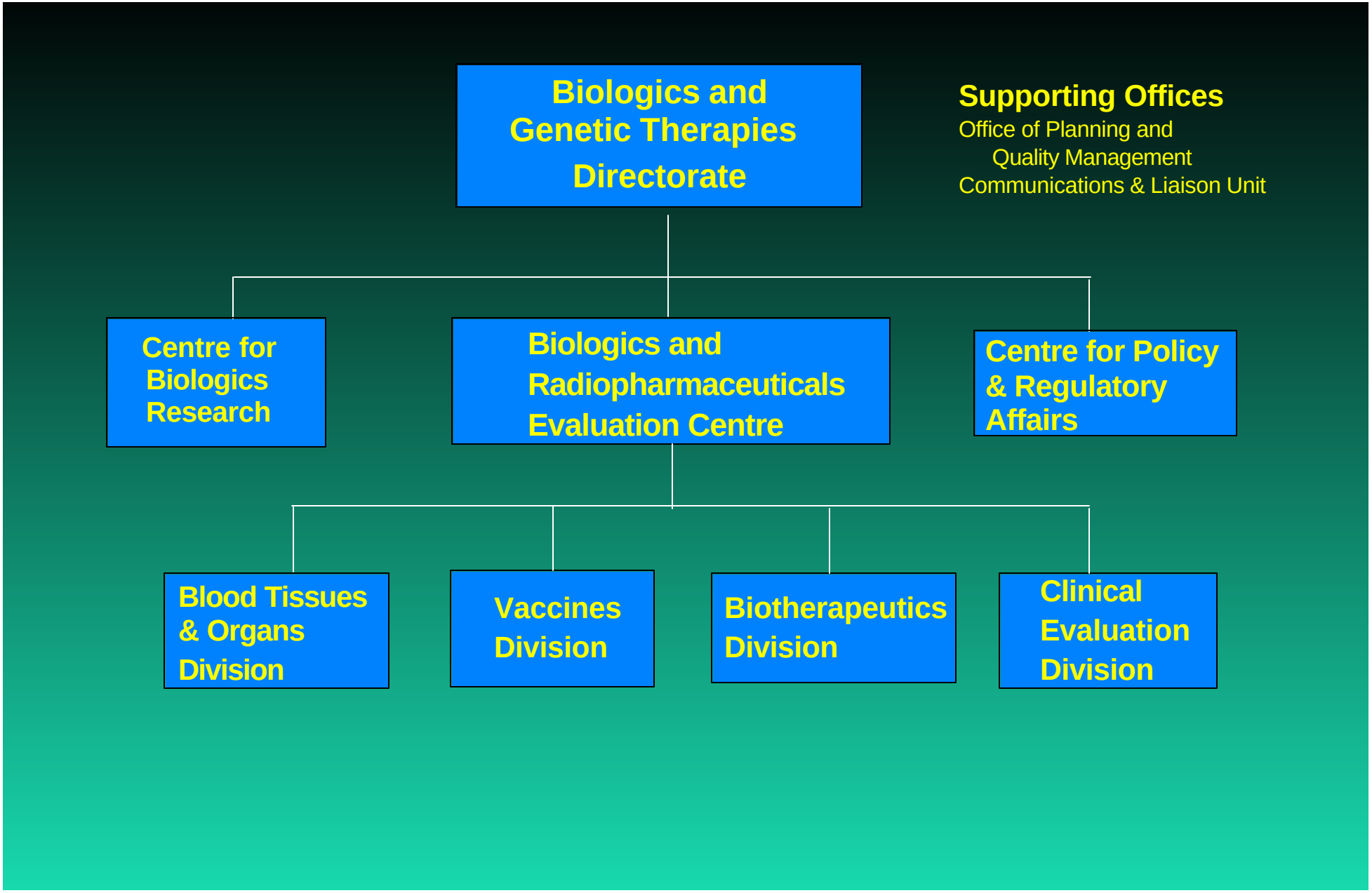


Supporting Offices

Office of Biotechnology & Science
Office of Regulatory and International Affairs
Office of Consumer and Public Involvement
Health Products and Food Litigation Secretariat
Office of Management Services

Regional Offices

Manitoba - Saskatchewan
British Columbia - Yukon
Atlantic Region
Nunavut - Ontario
Alberta - Northwest Territories
Quebec


Biologics and Genetic Therapies Directorate
Supporting Offices
Office of Planning and Quality Management
Communications & Liaison Unit
Centre for Biologics Research
Biologics and Radiopharmaceuticals Evaluation Centre
Centre for Policy & Regulatory Affairs
Blood Tissues & Organs Division
Vaccines Division
Biotherapeutics Division
Clinical Evaluation Division

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What is a drug?

- "Any substance or mixture of substances manufactured, sold or represented for use in:

  a) the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state or its symptoms, in human beings or animals

  b) restoring, correcting or modifying organic functions in human beings or animals

  c) disinfection in premises in which food is manufactured, prepared or kept"

Food and Drug Regulations, Part C: Drugs

- Division 1: Labelling, DIN and prescription requirements for all drugs
- Division 1A: Establishment Licensing
- Division 2: Good Manufacturing Practices
- Division 3: Radiopharmaceuticals (Schedule C drugs)
- Division 4: Biologics (Schedule D drugs)
- Division 5: Clinical Trials
- Division 8: New Drugs

"Biologics are Different"

Drugs isolated from, or manufactured using, living organisms present additional regulatory challenges compared to drugs that are chemically synthesized.

- risks associated with starting materials or adventitious agents
- inherent variability of products derived from manufacturing processes that use living systems
- difficulty in precisely controlling the manufacturing process
- sensitivity of the structure and activity of biological molecules to environmental factors
  - temperature, freeze-thaw, light, solution conditions
- product complexity affects the ability to characterize and test

What is a Biologic?

- Drugs listed in Schedule D of the Canadian Food and Drugs Act are referred to as biologics and are subject to the special regulatory controls for biologics set forth in Division 4 of the Food and Drug Regulations
- The Schedule lists drugs prepared from animal or human tissues or excretions from micro-organisms, whether "natural" or genetically engineered
- Includes vaccines, sera, blood and its derivatives, certain hormones and enzymes, allergenic extracts, monoclonal antibodies and rDNA products
- Some biological products prepared from micro-organisms are excluded from Schedule D; examples include antibiotics and products to replenish intestinal flora

Schedule D

- allergenic extracts
- anterior pituitary extracts
- aprotinin
- blood and blood derivatives
- cholecystokinin
- drugs obtained by rDNA procedures
- drugs from micro-organisms (except antibiotics)
- glucagon
- gonadotrophins
- human plasma collected by plasmapheresis
- immunizing agents
- insulin
- interferon
- monoclonal antibodies, their conjugates & derivatives
- secretin
- sensitivity discs and tablets
- snake venom
- urokinase

What is almost a Biologic?

- Products of types similar to those listed in Schedule D, for which there are special safety and quality concerns, are candidates for addition to the Schedule and are regulated as biologics; e.g., somatic cell therapies, cells and tissues which undergo extensive manipulation (therefore considered to undergo "manufacturing")

- Products that do not fit under the regulations for either biologics or devices will be controlled by a standards-based approach. For example, the "Canadian Standard on Cells Tissues and Organs Intended for Transplantation" which came into effect in January, 2003.

Approach to Regulation of Biologics

- Makes use of the powers available under the Food & Drugs Act and Regulations
- Involves an integrated approach using teams comprising clinical and C&M reviewers, laboratory staff, regulatory affairs staff and inspectors.
- Involves, submission review, laboratory testing of qualifying/consistency lots, on-site evaluation (OSE) of manufacturing facilities, and administration of a lot-by-lot release program

Laboratory Activities Within BGTD

Involve the product-line divisions of the Biologics & Radiopharmaceuticals Evaluation Centre (BREC) and the Centre for Biologics Research (CBR) and include:

- testing of consistency lots (pre-approval), including paper review of methods and batch documentation (BREC)
- lot-by-lot release program (BREC)
- test method development and modification (BREC)
- collaborative studies with other regulatory authorities (NIBSC, WHO) (BREC & CBR)
- relevant research on biological drugs (CBR)

On-Site Evaluation

The On Site Evaluation assesses the production process and the facility and their potential for impact on the quality and safety of the product

- conducted on-site at the manufacturing facilities
- focused largely on product-specific manufacturing issues but incorporate relevant GMPs
- lead inspector often accompanied by product specialist involved in C&M review, or a trainee inspector
- depending on GMP status of facility, the OSE may involve a GMP specialist (from inspectorate)

Rationalized Lot-Release Program

- in effect since 1995
- a resource-conscious approach
- categorization of products according to risk
- reduce unnecessary testing; focus on critical quality/safety

Rationalized Lot-Release Program

- Category 1: only products in clinical trials. An attestation that the product met all specifications is submitted by the sponsor on a "Faxback" Form (48-hr turnaround)

- Category 2: (includes all prophylactic vaccines) samples of each lot are submitted for testing against the C of A; focused on critical quality and safety tests

- Category 3: C of A reviewed; intermittent requests for samples to test

- Category 4: release automatic; Cs of A submitted in Annual Reports. *(Caveat: for all products formulated with human-derived excipients (e.g. albumin), Faxback Form is submitted providing lot numbers and confirming that all specificiations for product and human-derived excipient were met)*

To Market a Biologic in Canada

- A Notice of Compliance (NOC)
  - Review of chemistry and manufacturing data, and clinical data and facility information contained in a New Drug Submission (NDS)
  - Testing of consistency samples (3-5 lots)
  - Pre-approval On-Site Evaluation of manufacturing sites
- An Establishment License
  - is issued on the basis of evidence of GMP compliance
  - the distributor (holder of NOC) must have a Canadian Importer who holds an Establishment Licence

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Royal Commission on New Reproductive Technologies

- 1994 Report

- Origins in concerns about ethics of certain technologies and their commercialization; and the safety of products and procedures (sale of gametes, embros; surrogacy; issues of consent)
- Government response = draft legislation
- Also addresses:
  - ► embryonic stem cells (allows preparation from existing/residual embryos and licensed use)
  - ► human cloning (banned, including therapeutic cloning)
  - ► intentional germline modification (banned)

Regulatory Challenges I

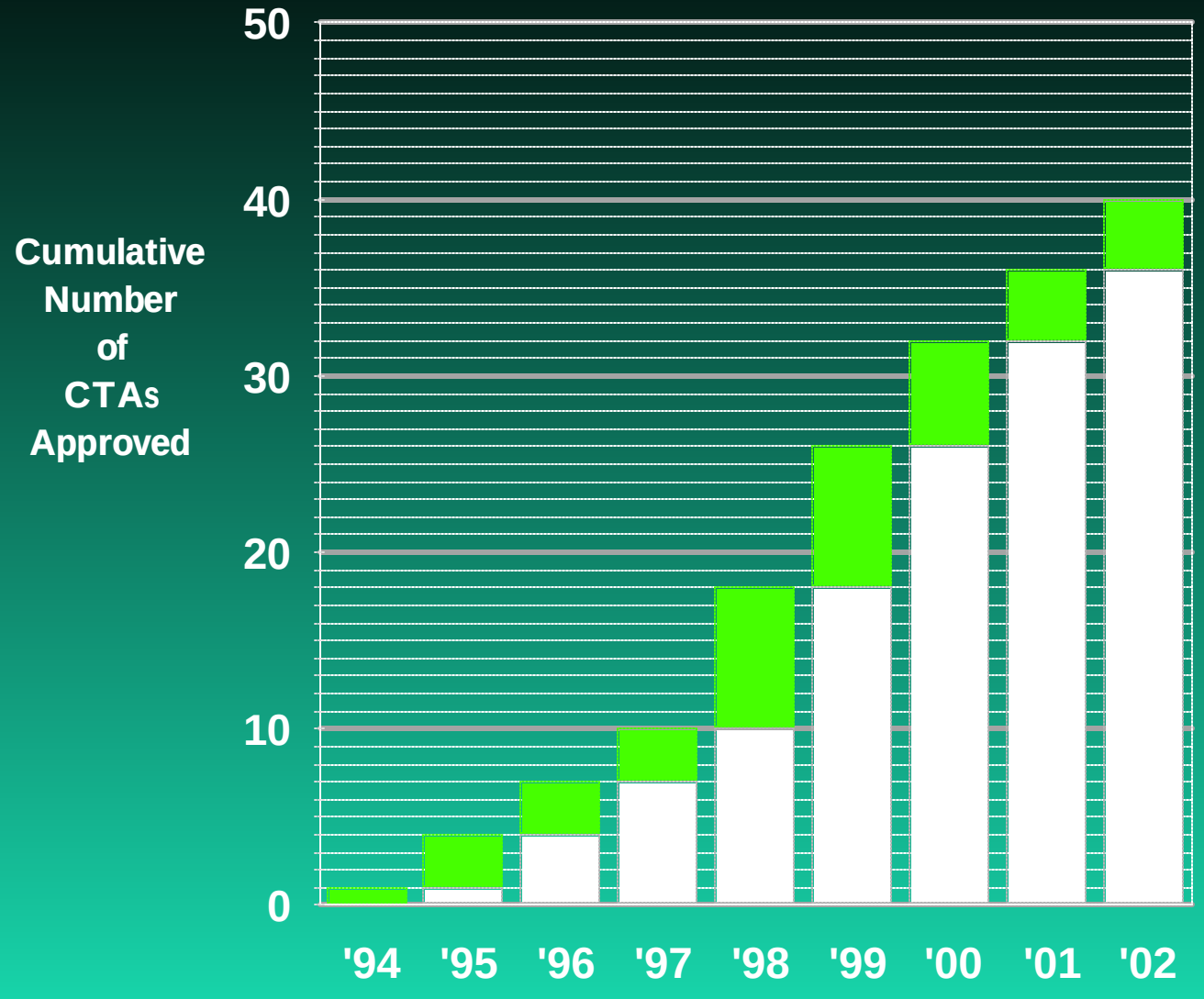
- Biogenerics
  - ►no US-type legislative issues
  - ►no generic biologics .... but we have a case-by-case regulatory approach to "subsequent-entry biologics" seeking approval with limited clinical data

- Drugs from transgenic animals and plants
  - ►are biologics
  - ►no specific regulations or guidelines
  - ►no regulatory gaps but need to resolve unique and shared responsibilities with other departments r.e. manufacturing sources

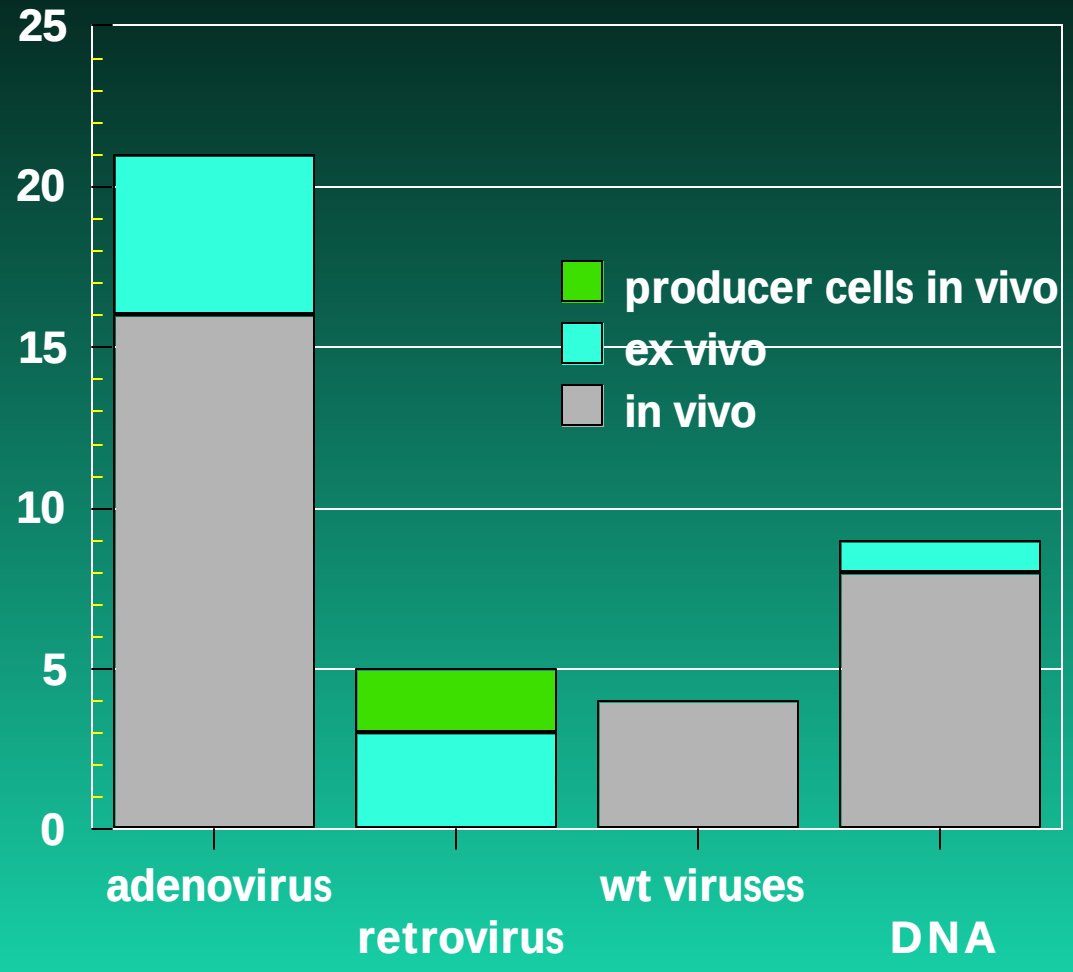
Regulatory Challenges II

- Gene therapy
  - ► expanding range of viral vectors and potential uses
  - ► no specific Canadian regulations or guidelines (no regulatory gaps and no problems yet but ....)
  - ► no national GT advisory committee ..... no problems yet, but might be useful for consideration of:
    - replication-competent vectors,
    - treatment of monogenic disorders,
    - treatment *in utero*,
    - risk tolerance for germline modification (accidental)

Growth of Gene Therapy in Canada



Gene Therapy Trials in Canada



Regulatory Challenges III

- Delays in product availability due to submission backlog, increasing workload, delayed filing
  - ► backlog (those submissions for which the review target has passed)
    - – results from a combination of: high workload, insufficient resources, depth of evaluation, priority designation
    - – will need special measures to clear, e.g.:
      - • reduced evaluation if product is widely approved elsewhere
      - • regulatory cooperation, e.g. use foreign report as 1st review
  - ► increasing workload
    - – international trend for biologics
    - – address via international harmonization & cooperation
  - ► delayed filing in Canada
    - – small market issue
    - – should be partially addressed by CTD

Biotechnology Pipeline

Category	# of Drugs
Cancer and related conditions	151
Infectious diseases	36
HIV infection/AIDS-related disorders	29
Heart disease	28
Neurological disorders	26
Other diseases	22
Respiratory diseases	20
Autoimmune disorders	19

Biotechnology Pipeline cont.

Category	# of Drugs
Skin disorders	14
Transplantation	14
Diabetes and related disorders	13
Genetic disorders	10
Digestive disorders	9
Blood disorders	8
Growth disorders	4
Infertility	4
Eye conditions	3

Conclusions

- Biologics regulation in Canada involves a carefully evolved and integrated approach
- The elements of the approach are typical of those used by many countries
- With a small population, limited resources and increasing workload, innovative strategies will be required for Canada to retain sovereinty in decision-making while coping with new technologies and many new biologic products