Canadian Perspective on Biologics Regulation; and Review of Gene Therapy Activity

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Presentation Outline

- **Regulation of Biologics**
- **Regulatory Challenges and Responses**
- **Legislative Renewal & Progressive Licensing**
- **Review of Gene Therapy Activities**

Regulatory Framework

- **Statutes (Acts): provides scope, and legal authority to make regulations**
- **Regulations: interpret the Act, provide general details on what must be done**
- **Guidelines: interpret and provide details of how to meet the regulations, allow flexibility and adaptation to change, faster and simpler to introduce (not legally binding)**

- **Policies: expand or modify interpretation of the regulations, provide a "quick fix" pending re-drafting of regulations (can be legally challenged); usually relax or simplify**

Canadian Food and Drugs Act

Definition of a Drug

...any substance or mixture...blah..blah..blah manufactured, sold or represented for use in:

a) the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or the symptoms thereof...blah..blah..blah;

b) restoring, correcting, or modifying organ functions...blah..blah;

c) disinfection...blah..blah..food is manufactured...blah..blah.

What are Biologics?

- **No current written definition in Canada**
- **Listed on Schedule D to the Food and Drugs Act (specifically or within a class)**
- **Generally derived from or through the metabolic activity of living organisms, natural or genetically modified**
- **Examples include: vaccines, blood and blood products, gene therapies, and protein therapeutics such as cytokines, hormones and MAbs**

Schedule D Drugs

- Allergenic Substances
- Aprotinin
- Cholecystokinin
- Drugs from microorganisms (other than antibiotics)
- Gonadotropins
- Immunizing Agents
- Interferon
- Secretin
- Drugs by r-DNA procedures
- Glucagon
- Human Plasma by plasmapharesis
- Insulin
- Monoclonal Antibodies
- Urokinase
- Snake venom
- Anterior pituitary extracts
- Blood and Blood Derivatives

Distinction between Natural Health Products and Biologics

- In general, not a NHP if listed on Schedule D
  - Not a NHP if product is specifically listed by name
  - Some products captured under certain group listings might be NHPs, e.g. some products of microorganisms
- NHPs must be suitable for self-administration (if intervention of a physician is advisable then it is not a NHP)
- If administered via puncturing the dermis it cannot be a NHP

Differences between Biologics and Chemical Drugs

- Starting material and some raw materials used for biologics are variable in nature (serum derivatives, enzymes, cell substrates).

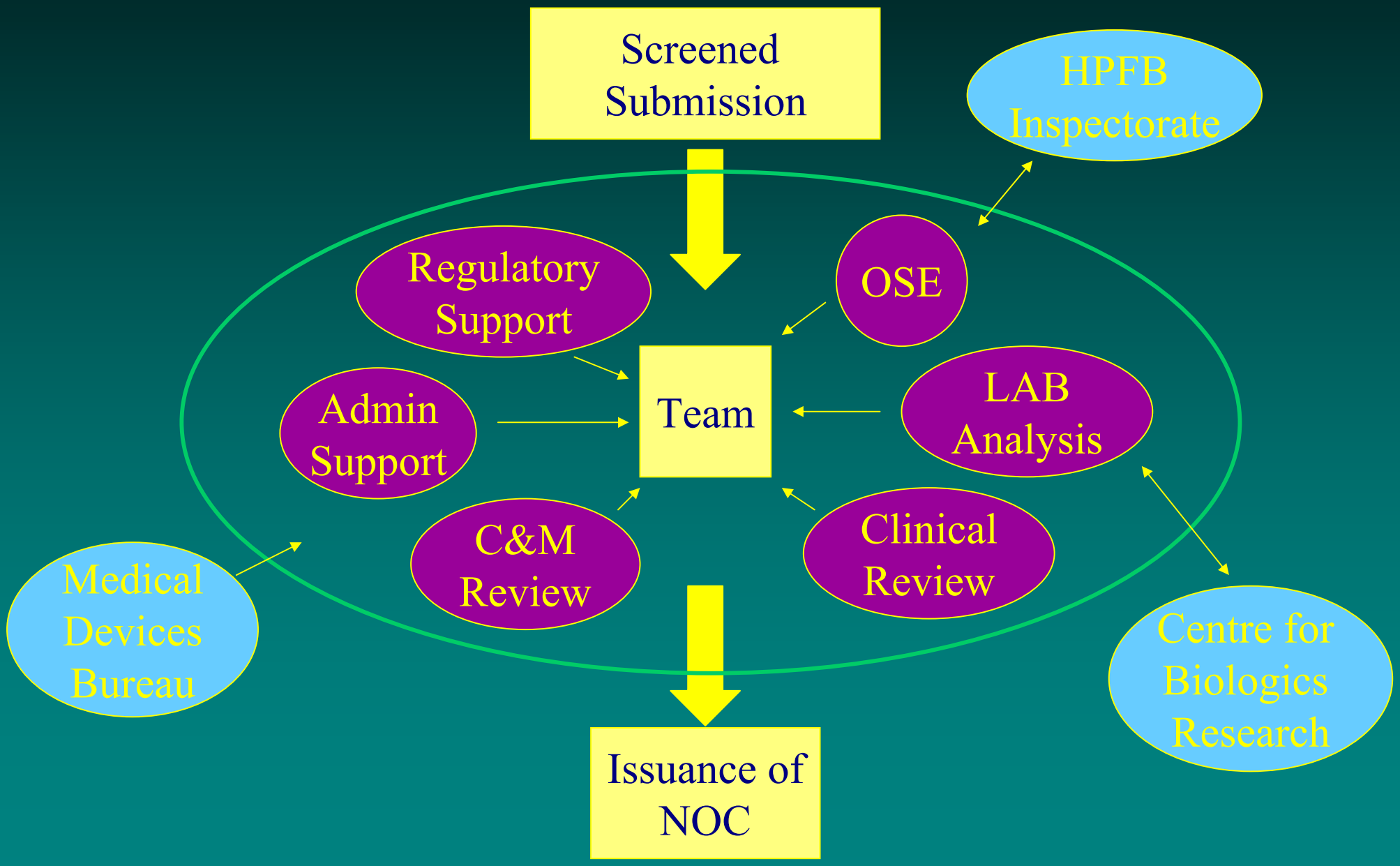
- Manufacturing processes are biological in nature and variable
  - procaryotic or eucaryotic cell systems
  - stages of manufacture are often carried out under conditions that cannot meet the same manufacturing standards as conventional pharmaceuticals
  - system of in-process controls required
  - aseptic processing
  - no terminal sterilization in container

- Complex structure of final product
  - molecular weight and structure may be undefined
  - composition may be undefined (vaccines)

Differences between Biologics and Chemical Drugs

- Test methods needed to characterize batches of the product are variable in nature
  - potency, purity and safety of most biologics cannot be adequately tested by chemical or physical means alone
  - bioassays have a high degree of variability / invalidity
- Quality cannot be established entirely by tests on the material in the final container

Submission Review Team



Laboratory Testing

- Addressed early in the review process
- Choose a subset of the release tests

  Release tests are chosen based upon

  - Probative/investigational value
    - Bioactivity, stability indicating HPLC analyses
  - Available resources
    - Equipment
    - Personnel

On-Site Evaluation

- Pre-approval inspection of the manufacturing facility.
- Product and process specific inspection rather than facility specific.
- Some obvious overlap with cGMP but this is not the primary focus.
- Both Drug Substance and Drug Product manufacturing facilities are subject to an OSE.

On-Site Evaluation

- Decision to conduct is based upon
  - **Experience with the manufacturer**
  - **Experience with the manufacturing process**
  - **Facility issues identified in the review**
  - **Laboratory testing problems**
  - **Known compliance problems at the facility**
  - **Not in production**

Lot Release Program

On-going Assessment of Biological Drugs to ensure Safety and Efficacy

Four assessment categories from full and complete testing through protocol review down to notification and tracking

Lot Release

- **a system of approval given for the release onto the Canadian market of a specific lot of biological product based upon certification that the lot meets appropriate in process controls and control tests on final products.**
- **such controls to be applied to the release of batches of the product have been decided at the time of licensing of the biological product (but may change).**
- **Lot release is necessary because of the complex nature of biological drugs.**
- **The Lot Release program has been rationalized based on a risk assessment model.**

Lot Release

- **Factors influencing the degree of assessment:**
  - **Product Indication**
    - **Age/health status/size of target population**
    - **Disease state & duration of treatment**
  - **Nature of the product**
    - **Source and level of control of the raw materials**
    - **Complexity, robustness and control of the process**
    - **Chemical/biological complexity of the DS and DP**
    - **Reliability/complexity of the methods used to evaluate identity, purity, and potency**

Lot Release

- **Factors considered in determining the degree of assessment:**
  - **Production history**
    - **Consistency of manufacturing**
    - **Changes in the incidence of reprocessing lots**
    - **Incidence and seriousness of lot failures**
  - **Inspection history**
    - **Major quality and safety issues at OSE or cGMP inspection**
  - **Testing history (manufacturer and BGTD)**
  - **Post-market experience**
    - **Adverse drug reactions (ADRs), product recalls/withdrawals**

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Challenges – workload vs resources

- 300-400 new biologics under development
- New types of products, and technologies
- Each approved NDS → 10 supplements and 30 NCs
- Financial resources will continue to be limited
- Competition for available expertise
- Different regulatory approaches will be required

Opportunities

- Availability of better medications; and treatments for currently unmet needs
- For regulators to show leadership/innovation; and to enhance trust/respect shown by the public & health sector

Challenges – public expectations

- Faster access to new medicines AND safer products with fewer adverse drug reactions (ADRs)
- Transparency r.e. regulatory decisions
- Access to more and clearer information along with greater responsibility for treatment decisions

Opportunities

- To better explain what we do and how we do it
- To win support for risk-based approaches
- For sharing of risks with end-users and practitioners

Challenges – ICH Q8, Q9, Q10

- Increased interaction/guidance during product development
- New approaches to evaluation of manufacturing process and facilities
- Risk managing the relaxation (?) of oversight

Opportunities

- Regulatory relief to industry, increased efficiencies
- Workload relief to regulators (on balance due to fewer submissions for manufacturing changes)
- Greater international harmonization

Challenges – Biosimilars

- Developing/rationalizing regulatory pathways
- Appropriate level of regulatory oversight
- How similar? How much new clinical data?

(Few in total but with public and political interest)

Opportunities

- Greater choice, cheaper products
- Incentive for new developments by innovators

Meeting the Challenges - Workload

- Harmonizing at ICH
- Taking steps to share/leverage effort and expertise
  - Developing MOU; Mutual Recognition Agreements
  - Parallel review project with TGA, Australia
  - "work-sharing" initiative
- "Rationalized" review

Meeting the Challenges - Regulatory

- Revising guidance on post-approval changes
  - More examples; more clarity; details on data to provide
  - Risk-rationalized lowering of level of submission
    - e.g.: S/NDS → NC; or NC → Notification/Annual Report
- Developing clear pathway for biosimilars
  - external consultation in February, 2008
- Planning/working to implement Q8, Q9, Q10
  - Educating/training reviewers
  - Needs coordinated approach at ICH
- Legislative renewal (all Health Canada activities)
- Progressive Licensing Framework (medicinal products)

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Legislation Renewal: Objectives and Scope

Objectives:

- Modernize, strengthen and integrate existing federal health protection legislation
- Provide overall policy direction for coherence and address gaps

Scope:

- A new legislative framework to replace and integrate:
  - *Food and Drugs Act* (1953)
  - *Hazardous Products Act* (1969)
  - *Radiation Emitting Devices Act* (1969)
  - *Quarantine Act* (1970)

The Motivating Policy Issues

- No expressly stated guiding principles, philosophy or values.
  - What are the principles that should be applied consistently across products?
  - No clear mandate for health surveillance and research
- No policy direction in risk-decision making grounded in legislation
  - What is our philosophy when addressing health risks, on issues such as consumer choice or the concept of precaution?
- Archaic enforcement powers
  - Current $5,000 maximum fine against drug manufacturer; no power to order manufacturer to take corrective action; way behind what exists in other federal legislation and internationally

The Motivating Policy Issues (cont'd)

- Gaps in What is covered:
  - No clear authority to deal with new and emerging technologies and certain health and safety related activities
  - limited authority to conduct post market surveillance (e.g. follow through to health outcomes)
  - Rules regarding Privacy not well suited to the public health context (e.g. sharing of information with agencies across levels of government)
  - No effective mechanism to categorize products between Acts (e.g. FDA-HPA-PCPA), or within same Act (e.g. FDA: food-drug-device?)
- Legal barriers to improving the efficiency and transparency of review processes
  - e.g. unclear rules in legislation regarding the confidentiality of commercial information

New Authorities To Be Sought:
To Collect and Use Confidential information

- In reviews of new drugs, medical devices, food and other products
- When seeking external advice
- To verify compliance with the legislation and regulations
- For reasons of public health and safety (i.e. significant risk to health)
- To collaborate with foreign jurisdictions for health and safety
- To endorse a standard or code of manufacturing or laboratory practice

New Authorities To Be Sought:
To Disclose Confidential information

With respect to:

- public health and safety (significant risk to health);
- details regarding products that would enable the public to make informed choices;
- existence of Clinical Trial Applications and ongoing clinical trials (drugs), Experimental Studies Certificates (devices), and Investigational New Drugs (veterinary);
- existence of submission filed and stage of review process
- regulatory decisions;
- changes made to products that would be relevant to the public and help them make informed choices;
- letters of authorization for sale of an approved drug for human or veterinary use in emergency treatment (SAP/EDRP);
- Health Canada's recognition of, or action against, a registrar.

Guiding Objectives of the Progressive Licensing Framework

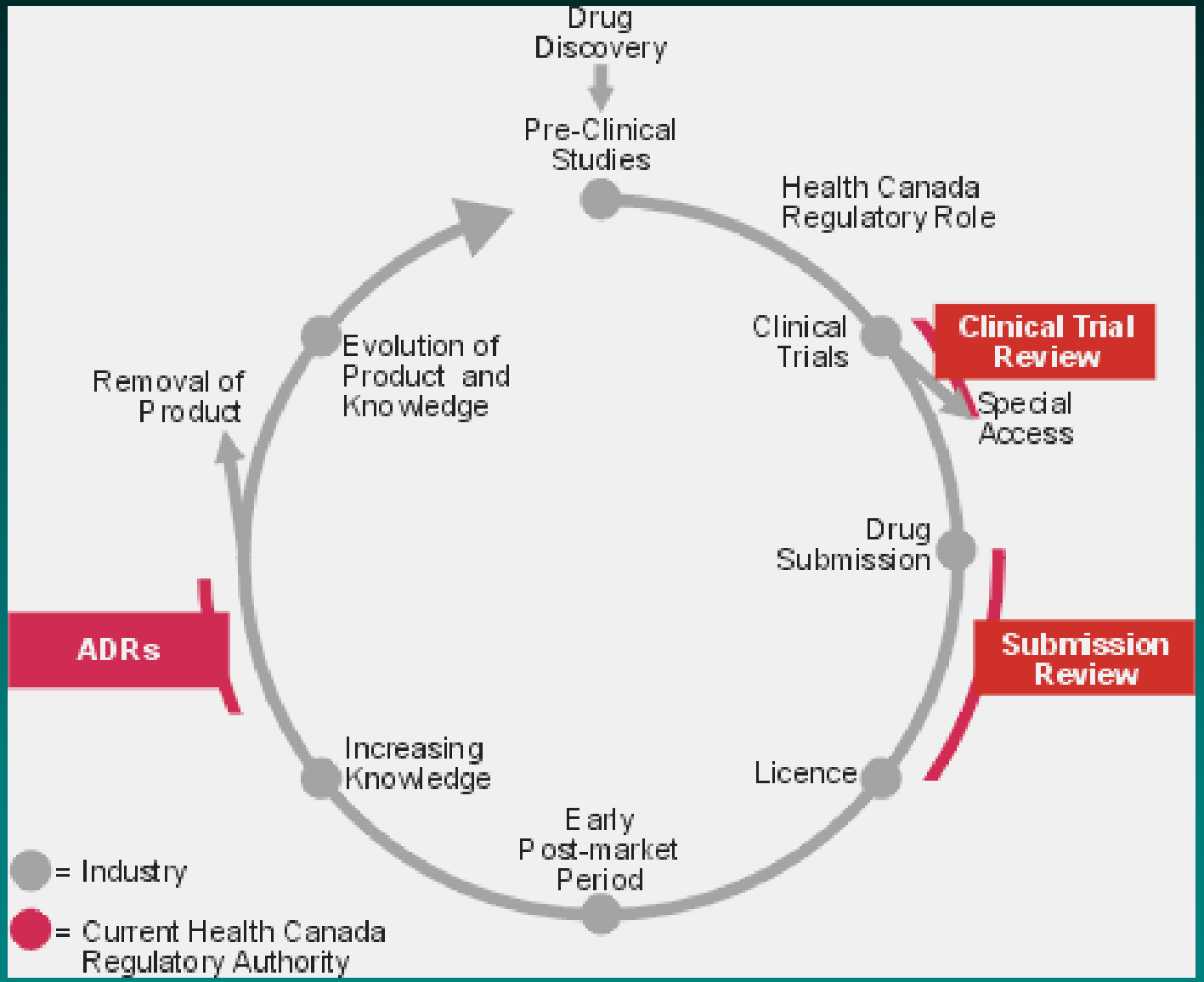
- PLF is guided by two continuing goals:
  - **protect the public from the marketing of unsafe drugs; and**
  - **support the safest use of drugs.**

- Three further supporting objectives have guided the design of PLF:
  - Align PLF with the system of health care in Canada to achieve positive health outcomes
  - Ensure that PLF enables Health Canada to implement best international regulatory practices and maintain appropriate oversight without unduly increasing regulatory burden; and,
  - Encourage and make best use of evolutions in the science of drug development and regulation.

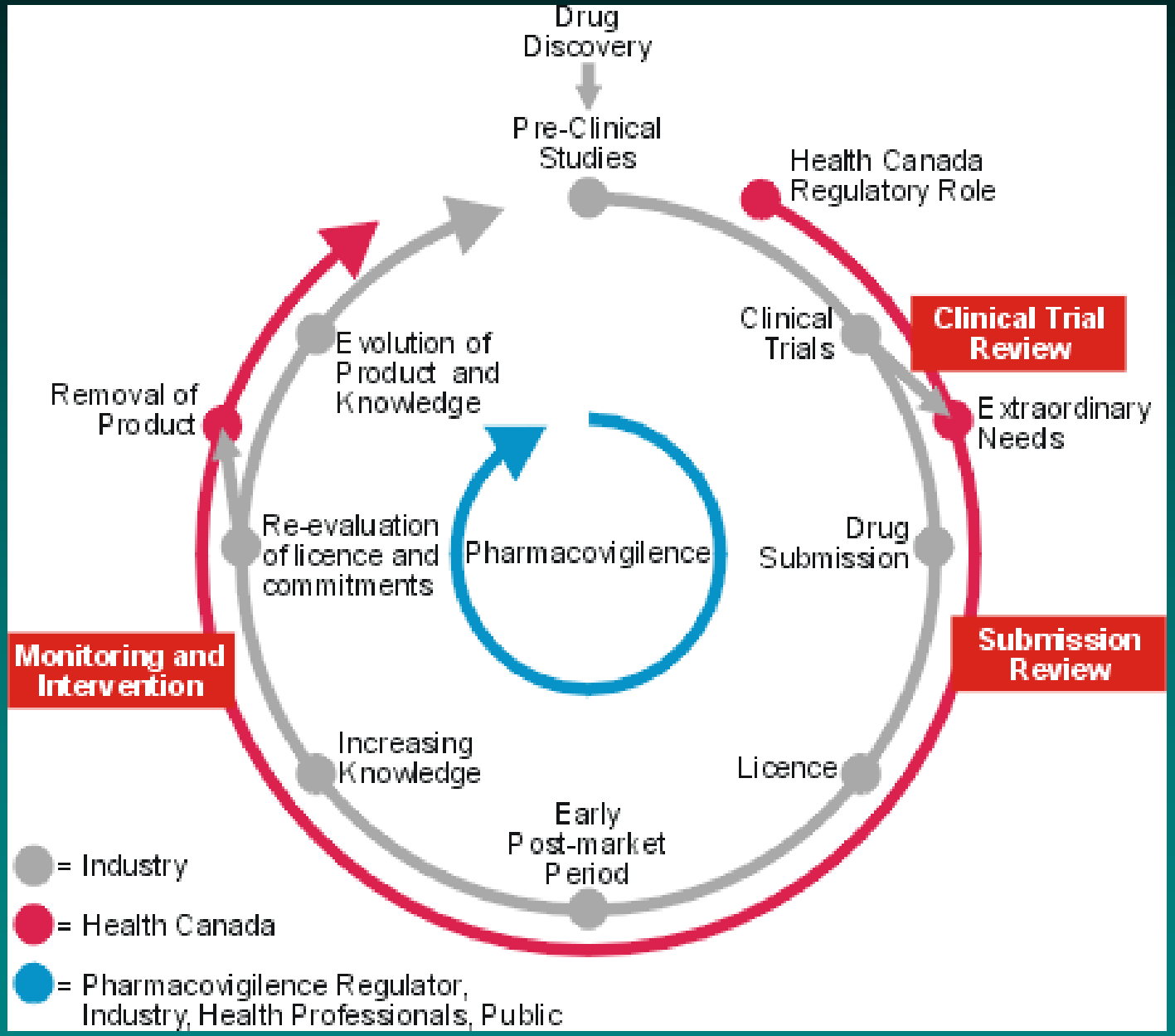
Life-Cycle

- The central concept of PLF is that over time there is a progression in knowledge about a drug;
- The emphasis of PLF is to identify opportunities within this progression over the life-cycle of a drug, rather than placing the regulatory focus only upon pre-market assessment;
- This represents a fundamental shift from the idea that the pre-market testing of a drug assures its safety and efficacy;
- PLF proposes that a drug should be evaluated throughout its life-cycle for its benefit-risk profile. There will be a requirement to file a life-cycle management plan.

Current Point-in-Time Process



Progressive Licensing Model



Approach

- PLF is being developed as a strategy for the modernization of the existing framework for the regulation of drugs (pharmaceuticals and biologics), under the *Food and Drugs Act and Regulations* (*FDA and FDR*)

- Changes to the *FDA* are required for the purposes of:
  - Eliminating provisions that have become outdated or that are not actively used by Health Canada
  - Providing explicit authority for the way in which certain products are currently regulated (such as medical devices) and for certain activities that Health Canada currently carries out.

Definitions

Therapeutic product:

- Introduce a definition for "therapeutic product" which should include any drug or device ('drug' and 'device' being themselves defined in the *Act*).

- This will provide the ability to regulate, through a life-cycle approach, a range of products broader than those falling within the existing definition of "drug", including drug/device combination products.

Authorizations

- Increased authority to create ongoing obligations on the market authorization holder; and that could be amended, suspended or cancelled

- Regulation-making powers respecting the issuance, amendment, suspension and cancellation of market authorizations, including the imposition of obligations relating to:
  - Pre-submission meetings
  - Registration and disclosure of clinical trial information
  - Post-market studies
  - Pharmacovigilance activities
  - Reassessments
  - Changes to product labels
  - Risk Communications

Authorizations

- Regulation-making power respecting the risk-based classification of different types of therapeutic products

- This will allow us to set submission requirements and impose obligations on market authorization holders based on the level of risk associated with the type of therapeutic product

Miscellaneous

- Employee immunity clause to protect employees of Health Canada against liability arising from decisions made as part of the product review process.

- Reporting from institutions: Integrate into the *Act* a mechanism for increasing reporting of serious adverse drug reactions by institutions.

- Compliance and Enforcement: increase penalties, authority to recall

- Openness and Transparency: enhance information sharing capacities

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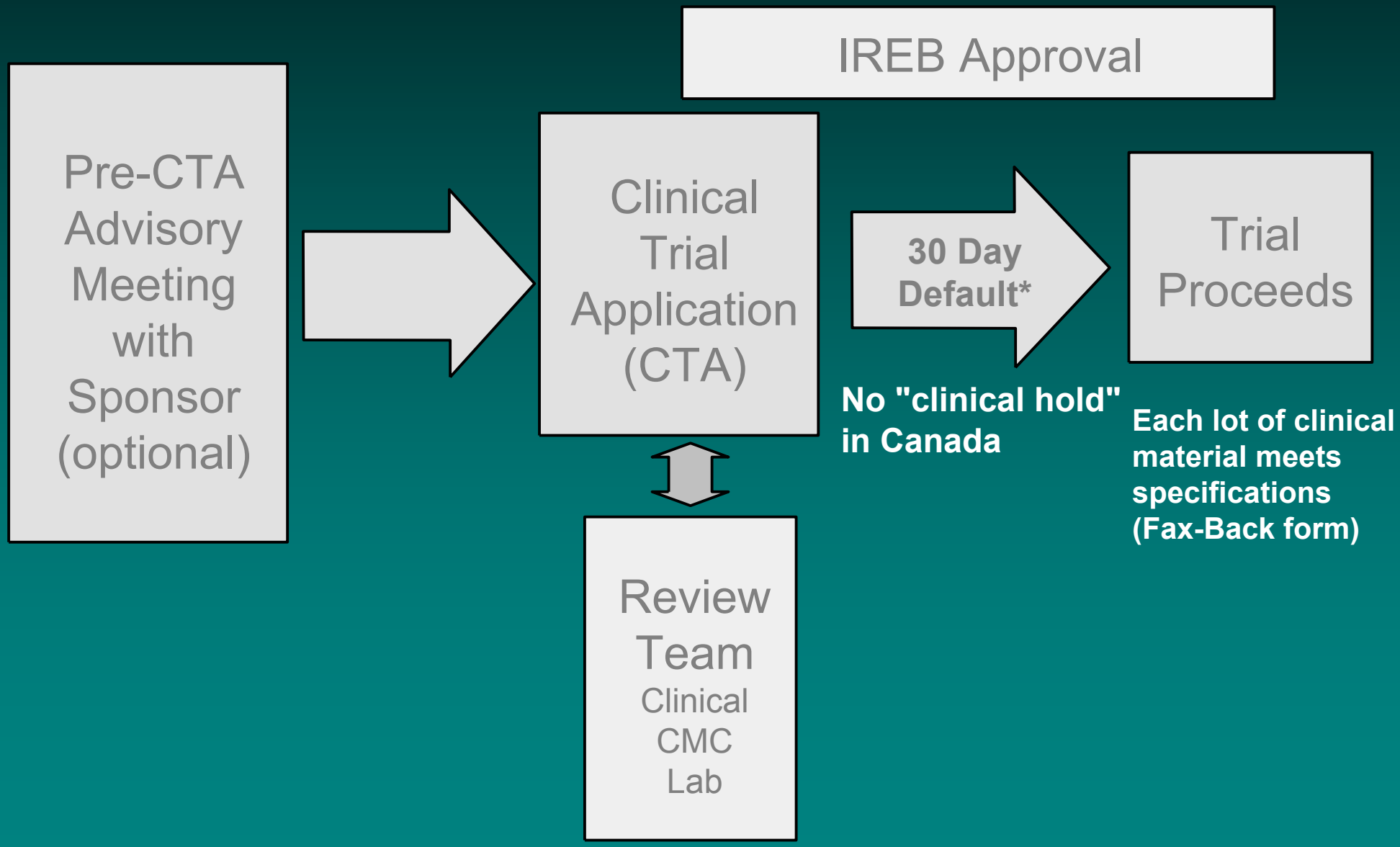
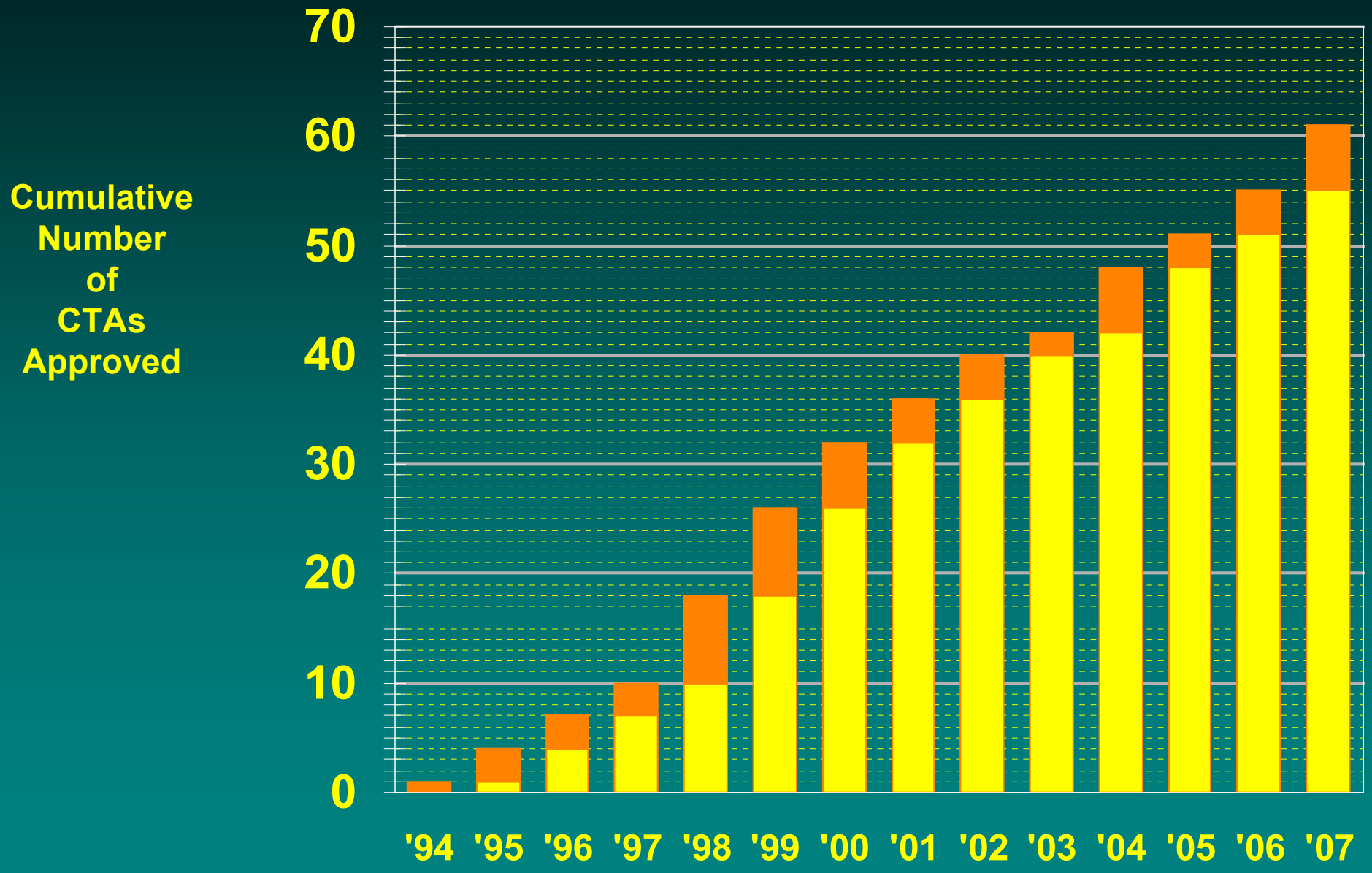
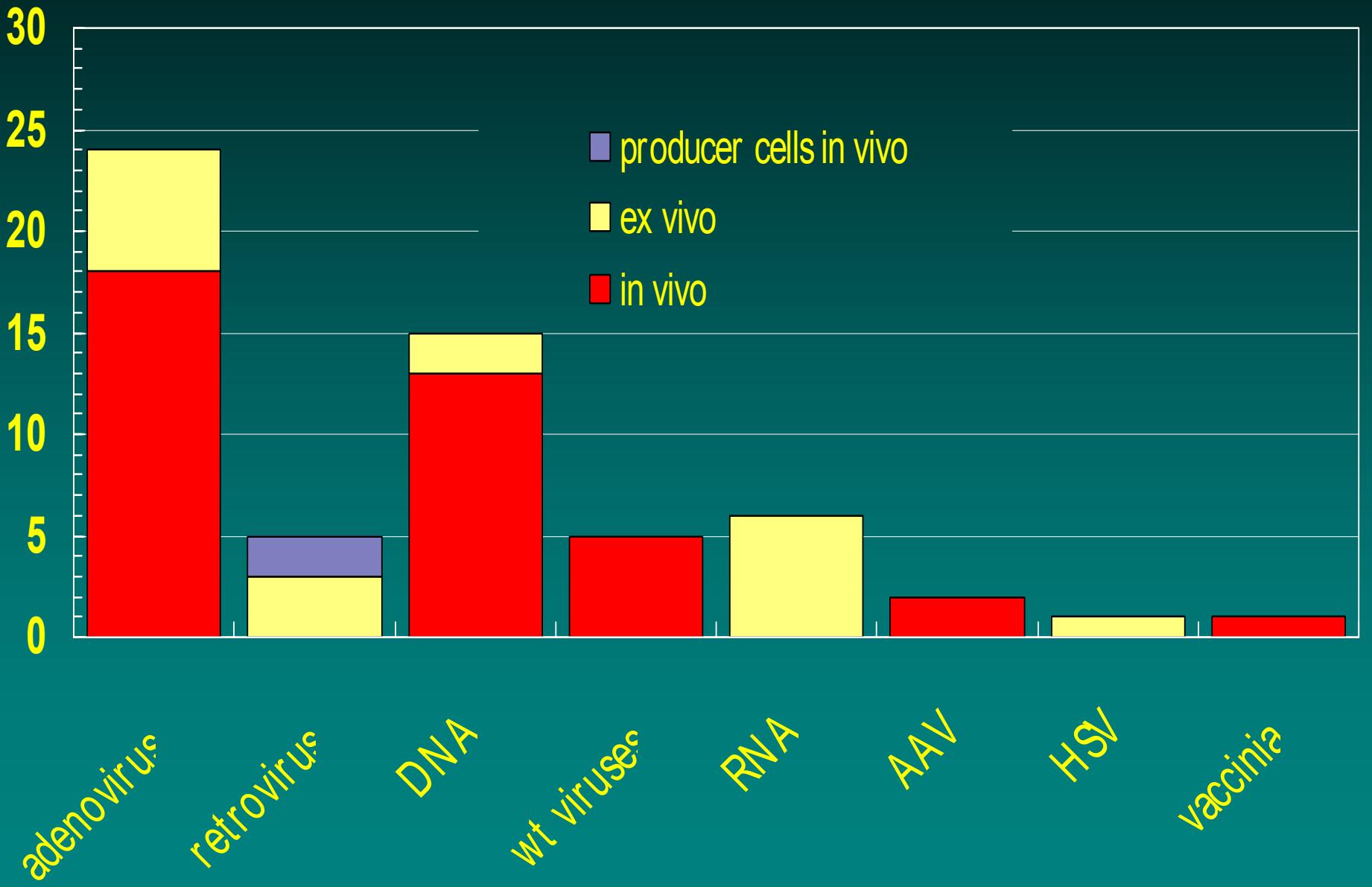
Regulatory Process for Clinical Trials



Growth of Gene Therapy in Canada



Gene Therapy Trials in Canada I



Gene Therapy Trials in Canada II

	number and type of vectors used							
	16 adenovirus	3 retrovirus	7 DNA	2 wt viruses	RNA	2 AAV	1 HSV	1 vaccinia
indications	carcinomas: breast liver prostate ovary bladder NSCLC SCCHN metastatic melanoma malignant myeloma AML CAD prophylactic HIV vaccine	glioma carcinoma of breast metastatic melanoma multiple myeloma *BMT (mdr)*	metastatic Solid tumours metastatic melanoma PVD CAD multiple sclerosis pulmonary arterial hypertension BMT *(neo)*	metastatic solid tumours carcinoma of prostate colorectal cancer	renal cell carcinoma HIV infection chronic lymphocytic leukemia	rheumatoid arthritis monogenic lipoprotein lipase deficiency	metastatic melanoma	malignant melanoma

Gene Therapy

Regulatory Comments I

- Canada is consistent with the international community in the regulation of gene therapy
- Canada has experienced significant growth in gene therapy clinical trials
- Regulatory and ethical challenges have been few due to the serious and often terminal nature of the diseases treated

Gene Therapy

Regulatory Comments II

- Careful attention is paid to minimizing the chance of third party exposure to vector
- Germ-line gene transfer is prohibited by law in Canada
- There are no gaps in regulation