Modernization of Legislation and Regulations: How does it support Product Vigilance?

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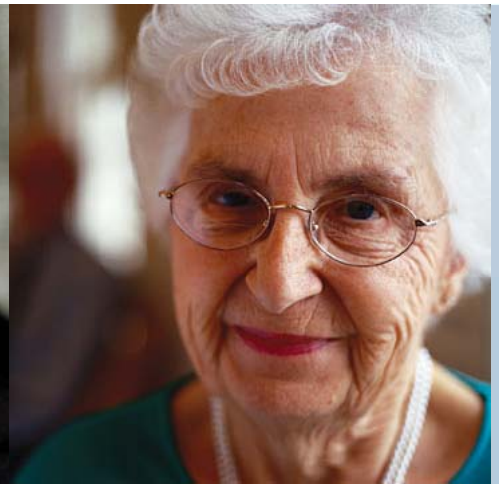


Canada

Presentation Objectives

- Describe the current regulatory system in Canada, and its gaps
- The need to modernize
- Product Lifecycle Approach with a highlight on Product vigilance
- Former Bill C-51 and post-market authorities

Product vigilance – key to effective regulation of therapeutic products

- The effective regulation of therapeutic products is an essential public health activity that protects and promotes the health and safety of Canadians.
- The current regulatory framework for therapeutic products – particularly pharmaceuticals and biologics – is outdated and does not meet current (future) needs.
- Our goal: to modernize Canada's framework for the regulation of health products
- Early in its development, project proposed a "lifecycle approach" to regulating drugs (Concept Paper, 2006)
- This includes the incorporation of regulations and activities that will support product vigilance

Pharmacovigilance – no longer “post-market” only

- In the past, pharmacovigilance has been viewed as a post-market activity, but regulators and manufacturers are now incorporating planning for pharmacovigilance earlier in the lifecycle of drugs.
- This early planning is recognized in documents such as ICH E2E and the template for risk management plans used in the European Union.
- This has been recognized since the inception of the PL Project, and was incorporated into the drafting considerations for the former Bill C-51.

Regulating Drugs in Canada – The *Food and Drugs Act*

- Main legislative instrument is the *Food and Drugs Act*
- Includes food, drugs, devices, cosmetics
- “Drugs” encompasses
  - Pharmaceuticals
  - Biologics
  - Radiopharmaceuticals
  - Natural health products
  - Cells, tissues, organs, blood

Existing *Act* and *Regulations*

The *Food and Drugs Act* (FDA, 1953) is a broad statute that provides the coverage for a number of sets of regulations governing a wide range of products:

- *Food and Drug Regulations (*the original set of regulations, 1960's*)*
- *Medical Device Regulations (1998)*
- *Natural Health Product Regulations (2004)*
- *Safety of Cells, Tissues and Organs for Transplantation Regulations (2007)*
- *Cosmetic Regulations (2004)*
- *Processing and Distribution of Semen for Assisted Conception Regulations (1996)*
- *Marihuana Exemption (Food and Drugs Act) Regulations (2003)*

How we regulate health products now

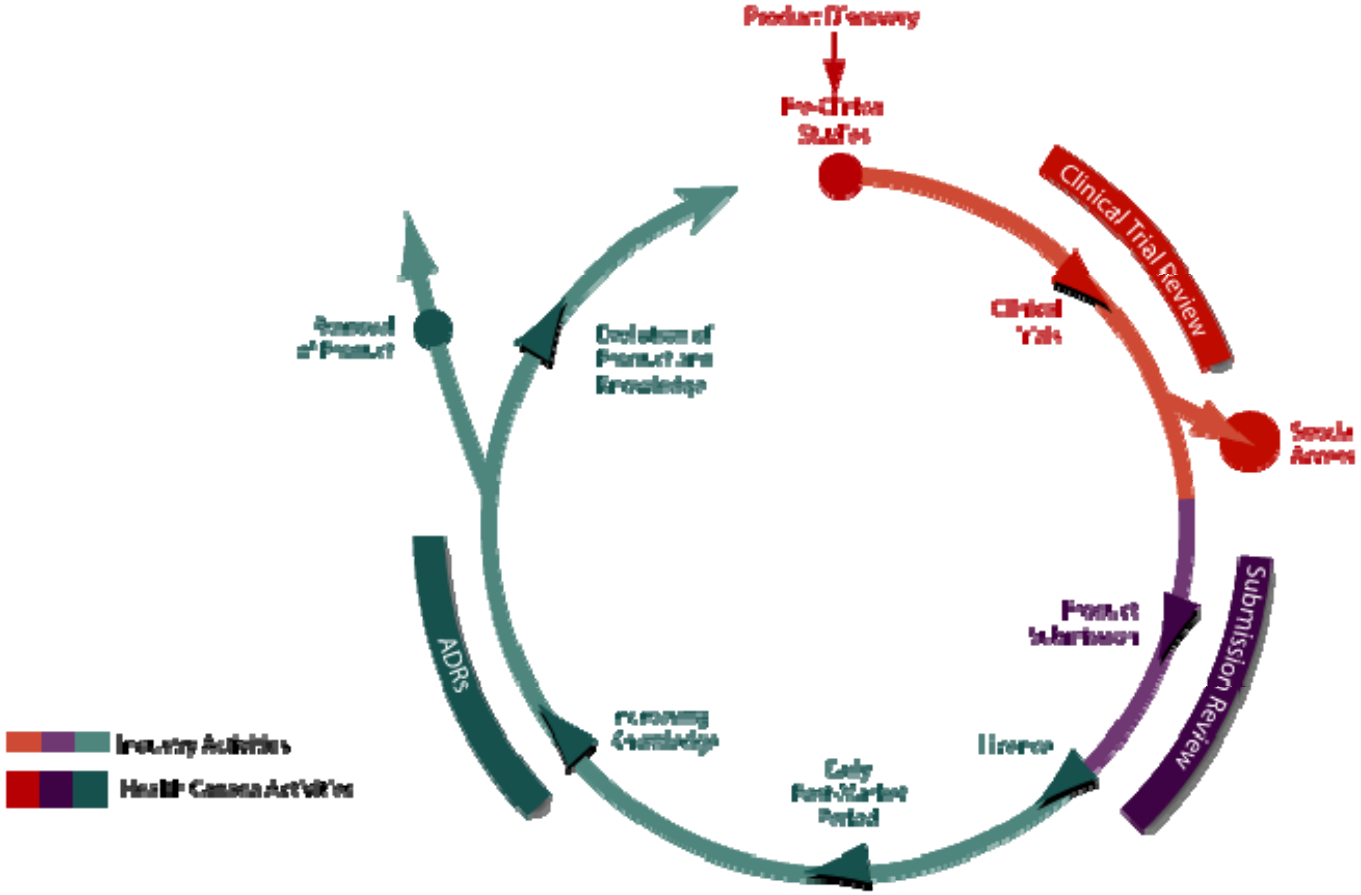
Under the *Act* and the *Regulations*, Health Canada:

- Reviews products prior to giving authorization or approval according to the applicable regulations
- Reviews clinical trial applications – drugs, devices, NHPs
- Requires the submission of adverse drug reactions/problems from manufacturers
- Issues establishment licenses to those who manufacture products

How we regulate health products now

- Original focus was on preventing adulteration of products, manufacture in unsanitary conditions, fraudulent labels/advertising
- Last significant revisions for drugs was done in the 1950's and 60's-thalidomide
- Focus was on collection and assessment of information prior to marketing of products
- Few abilities with respect to the post-marketing period related to adverse reaction reporting

Regulating Drugs in Canada – the current system



Need for modernization

- Recognition of the limitations of “pre-market” datasets
  - Exclusion of patients from clinical trials
  - Lack of investigations in certain patient populations
  - Do not detect uncommon or rare adverse events
  - Lack of “real-world” safety and effectiveness data

- Limitations of passive surveillance activities to detect and verify risks
- Modernization efforts in other regulatory jurisdictions
- Increased scrutiny of regulatory activities with respect to timeliness of decisions, openness and transparency

Need for modernization

- Pattern of disease and product use have changed – Canadians are living longer with chronic conditions
- Highly educated patient and consumer groups who want to be informed and involved
- Health care practice has evolved – patient/professional partnerships, “new” professional groups
- Our role as a regulator has changed – more than just a “gatekeeper”, higher expectations
- We have adopted of best practices and new methods of post-market surveillance, but this is suboptimal without regulatory support

International Developments

European Union

- New pharmaceutical legislation introduced in 2004, new pharmacovigilance proposals in 2007
- Directive 2001/83/EC, Regulation 726/2004, Regulation 507/2006
- Market authorization based on positive benefit-risk balance
- Ability to issue conditional market authorizations
- Requirements for risk management systems
    - Safety specification
    - Pharmacovigilance activities
    - Risk mitigation activities

International Developments

United States

- Food, Drugs and Cosmetics Act
- Institute of Medicine Report on Drug Safety released 2006
- FDAAA passed September 2007
  - Enhanced authorities regarding postmarket safety of drugs
  - Ability of Secretary to require postmarket studies and clinical trials
  - Ability of Secretary to require labelling changes
  - Ability of Secretary to require Risk Evaluation and Mitigation Strategy

Product Lifecycle Approach – Framework Objectives

The primary objectives of the framework itself are:

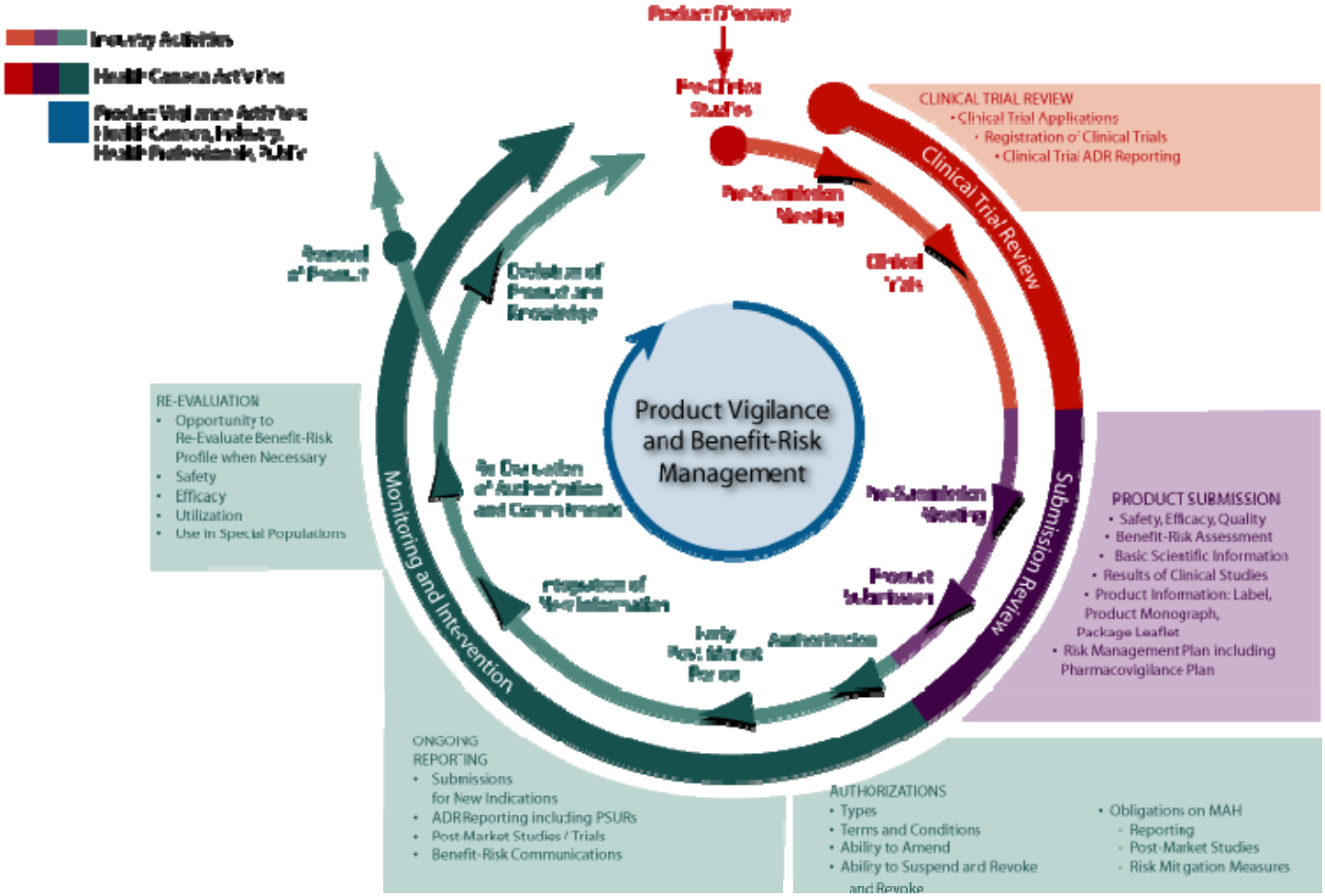
- To protect the public from the marketing of unsafe health products; and
- To support the safest use of health products.

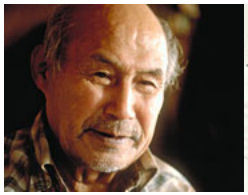
Product Lifecycle – Framework Objectives

Three supporting objectives:

- Better align the regulatory framework with the systems of health care in Canada to achieve positive health outcomes;
- Ensure that the new regulatory structure 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 product development and regulation, including incorporation of post-market data.

Lifecycle Approach Model






Bill C-51 - *An Act to amend the Food and Drugs Act*

- April 2008, Bill C-51 was introduced in the House of Commons
- Proposed amendments to the *Food and Drugs Act* would support new regulations for health products and food, including:
  - Authorization structures with terms and conditions
  - Enhanced post-market surveillance requirements
  - Modern enforcement and compliance powers
- Bill C-51 “died” on the order paper with the dissolution of Parliament in fall 2008
- Intent is to reintroduce proposed legislation as reasons for modernization are still valid

Bill C-51 - *An Act to amend the Food and Drugs Act*

- Bill C-51 contained a number of new proposals that were intended to support ongoing product vigilance by manufacturers, and Health Canada.
- To ensure that information will be collected, assessed, and communicated on an systematic and ongoing basis over the life-cycle of a product.
- The objective of ongoing assessment is to support the safest and most effective use of therapeutic products – minimize risks and maximize benefits.

Legislative and Regulatory Modernization and Product Vigilance

Market Authorizations

- Designed to provide a mechanism through which Health Canada can regulate a range of therapeutic products
- Ability to tailor the appropriate amount of continued regulatory oversight to the nature and risk of the product
- The need for specific vigilance activities will be included as part of the assessment of the benefits and risks, and included on the authorization

Legislative and Regulatory Modernization and Product Vigilance

Market Authorizations

- Market authorizations may be issued if person has established that the benefits associated with the product outweigh the risks

- Applicable regulation-making authorities
  - respecting the circumstances in which the Ministers is bound or ceases to be bound by statements made in writing to applicants for or holders of authorizations (pre-submission meetings)
  - respecting applications for, or the issuance, amendment, suspension revocation, or transfer of authorizations
  - specifiying terms and conditions
  - establishing classes of authorizations

Legislative and Regulatory Modernization and Product Vigilance

Regulations respecting applications for authorizations

- Regulations that describe what must be included in an application could include:
  - Inclusion of a pharmacovigilance/risk management plan for new chemical entities that have not previously been marketed in Canada, and for new indications
  - Summaries of pharmacovigilance activities/outcomes that have been conducted in other countries
  - Ability of Minister to require pharmacovigilance/risk management plans
- Basic elements of a pharmacovigilance/risk management plan would be outlined in regulations

Legislative and Regulatory Modernization and Product Vigilance

Market Authorizations

- Market authorizations can be subject to terms and conditions that are prescribed by regulations
- Applicable regulation-making authority - specifiying terms and conditions
- This provision would be used to enable regulations that will generally apply to all drugs, for example:
- Notification of a formulation change
  - Notification of change in regulatory status in another country,
  - Routine reporting of adverse drug reactions, such as those which currently exist in the *Food and Drug Regulations*
- Unique terms and conditions can also be applied to a market authorization, such as further investigations

Legislative and Regulatory Modernization and Product Vigilance

Power to require information

- purpose: to ensure that information necessary for the ongoing evaluation of the benefits and risks of therapeutic products can be obtained
- necessary to address those circumstances that would not be already addressed through the terms and conditions of an authorization or licence.
- Corresponding regulations could permit the Minister to specify the types of information that could be requested (for example: results of clinical trials or other studies, adverse drug reaction reports, and risk communications issued in other regulatory jurisdictions),the time frame for the delivery of such information, how the information should be submitted, and to whom the information should be delivered.

Legislative and Regulatory Modernization and Product Vigilance

Power to require tests or studies, etc.

- ensure that an analysis of the need for vigilance and other post-market activities is performed prior to marketing;
- clearly describe the reasons for, and expectations of, vigilance activities for industry, the regulator, health care professionals, patients, and other stakeholders;
- ensure timely reporting to HC
- ensure that the results are incorporated into overall benefit-risk assessments so that accurate information can be communicated health care professionals, consumers and patients.

Legislative and Regulatory Modernization and Product Vigilance

Power to require labels to be revised

- will ensure that labels of therapeutic products, which facilitate the safest use of the product, contain accurate and up-to-date information about the risks and benefits of the product.
- will support the timeliness of label/information changes
- Corresponding regulations would outline the circumstances and the procedure through which the Minister could direct the holder of a market authorization to make revisions to therapeutic product labels, including product monographs.

Legislative and Regulatory Modernization and Product Vigilance

Power to require reassessment

- opportunity to have a “second look” at all of the benefit-risk information that has been generated about a product, including that derived from vigilance activities
- need for a reassessment could be identified at the time of marketing, after the completion of a post-market study, or after the identification of a new safety concern.
- regulations could outline the circumstances and the procedure under which the Minister could require a market authorization holder to conduct and submit a reassessment of a product’s benefit-risk profile
- regulations could allow the Minister to specify what kind of information should be included in the benefit-risk reassessment, how it should be provided, to whom it should be provided, and the time frame for submission.

Legislative and Regulatory Modernization and Product Vigilance

Power to disclose risk and benefit information

- will support HC in advising the public of emerging information, especially risk information, in a timely and appropriate manner.
- New risk information frequently identified through vigilance activities
- regulations could outline the circumstances under which the Minister would disclose information about a product's benefits and risks, including:
  - new safety information that should be considered by health care professionals and patient in the use of the product
  - withdrawal of a product from the market
  - new contraindications or warnings included in the product label
  - reassessment of the product's benefit-risk profile

Legislative and Regulatory Modernization and Product Vigilance

Regulation-making authority regarding pre-submission meetings

- enable regulations to be made for pre-filing meetings and advice to support the ratification of scientific and regulatory positions before extensive
- applicants would not be required to seek pre-filing advice or a pre-filing meeting, but would have the option to do so to receive either scientific or regulatory clarity.
- Early opportunity to discuss possible vigilance activities and requirements, including need for RMP

Legislative and Regulatory Modernization and Product Vigilance

Conclusion

- Explicit recognition that pharmacvigilance activities begin early in product development and continue throughout the product lifecycle
- Former Bill C-51 contained a number of provisions that directly support a lifecycle approach and vigilance activities – these provisions received broad stakeholder support
- The implementation of a new framework will involve revising current processes to fully incorporate a lifecycle approach to product vigilance

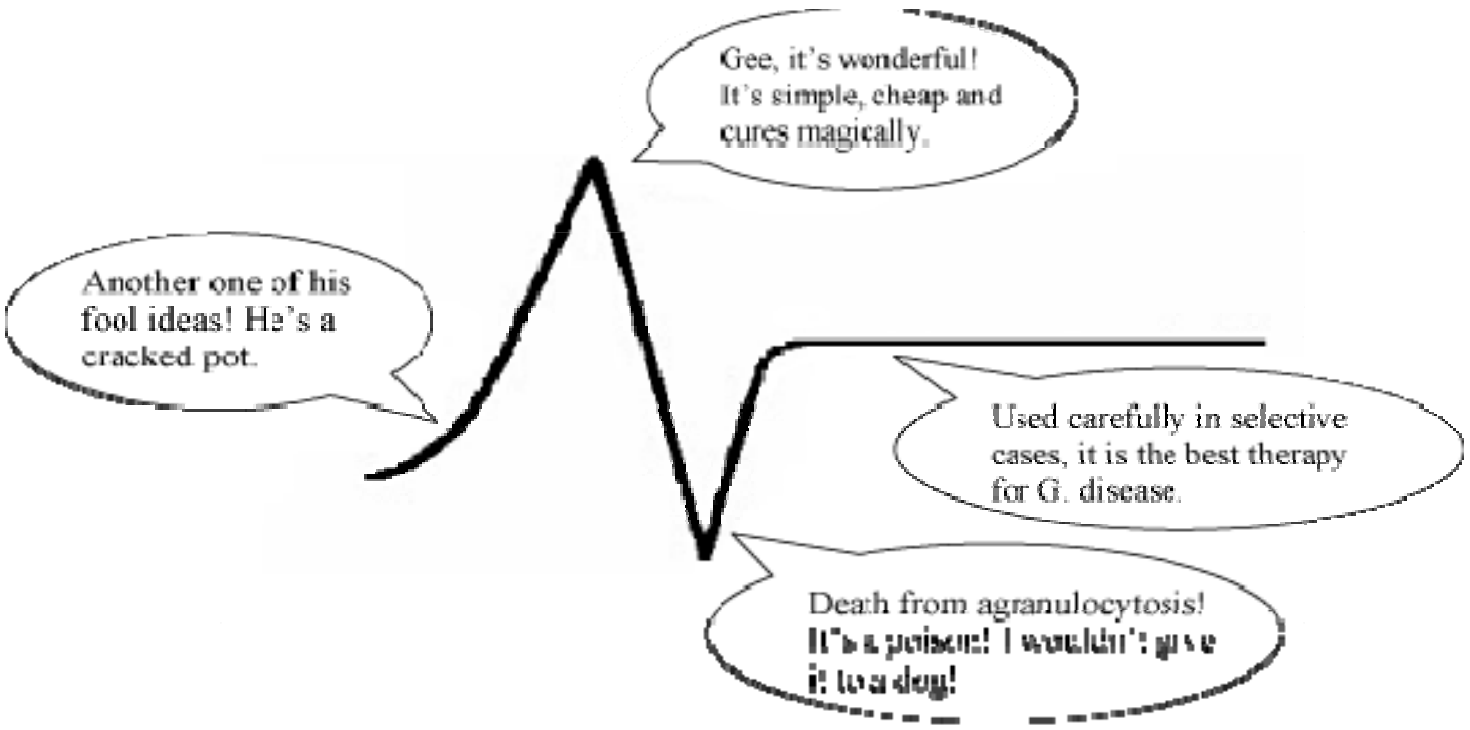


Figure 8-4 Oscillations in the development of a drug. (From Williams, R.H.: The clinical investigator and his role in teaching, administrating, and the care of the patient. J.A.M.A., 156:131, 1954)