Legislative and Regulatory Modernization for Therapeutic Products

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Presented at: Drugs in Pregnancy and Lactation Symposium, June 4, 2010, Toronto, Canada

ABSTRACT

This presentation is intended to show how the work coming from scientists, physicians, and other healthcare professionals is incorporated into the regulatory assessment of therapeutic products in Canada. One of the primary objectives within the regulatory environment is to provide information back to healthcare professionals and patients in order to help them make informed decisions. The current regulatory system for health products in Canada and why it needs modernization is addressed; a "lifecycle approach" to the regulation of health products is presented; the Food and Consumer Safety Action Plan and Bill C-51, a bill to amend the Food and Drugs Act is reviewed; and the challenges and opportunities for Canada and its fellow regulators are examined.

Introduction

It is exciting to be able to bring policy and regulatory work to the scientific community! This presentation is intended to show how the work coming from scientists, physicians, and other healthcare professionals is incorporated into the regulatory assessment of therapeutic products, and as a result gets solid information back to healthcare professionals and patients. Helping healthcare professionals and patients to make informed decisions is one of the primary objectives.

The current regulatory system for health products in Canada and why it needs modernization will be addressed; a "lifecycle approach" to the regulation of health products—where we would like to go—will be presented; the Food and Consumer Safety Action Plan and Bill C-51, a bill to amend the Food and Drugs Act, will be reviewed; and the challenges and opportunities for Canada and its fellow regulators will be examined.

Regulating Therapeutic Products in Canada - The Food and Drugs Act

The main legislative instrument for medications in Canada is the Food and Drugs Act, enacted in the early 1900s. It includes food, drugs, devices, cosmetics; and some key sets of regulations are:

- Food and Drug Regulations (includes clinical trial regulations),
- Medical Device Regulations,
- Safety of Cells, Tissues, and Organs for Transplantation Regulations.

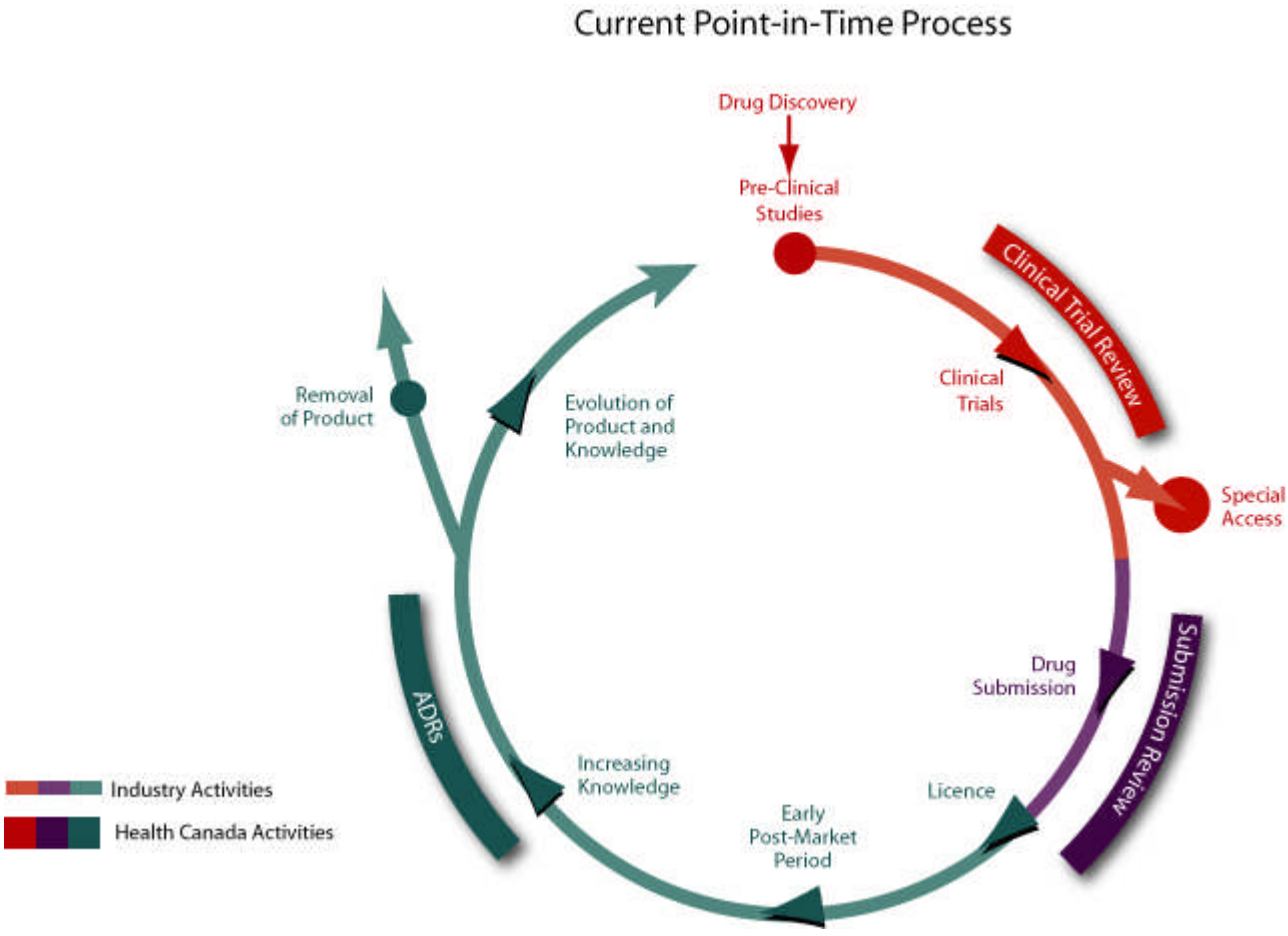
Under the current Act, "drug" encompasses products such as pharmaceuticals, biologics, radiopharmaceuticals, cells/tissues/organs, and blood and blood components. It is through the Act and its Regulations that the Health Products and Food Branch of Health Canada has the mandate to regulate these products. The original objectives of the Act were to prevent adulteration of products, manufacture in unsanitary conditions, and fraudulent labelling and advertising. The last significant revisions to the Act as regards drugs were made in the 1950s and '60s subsequent to experiences with thalidomide and other products. The focus at that time was on collection and assessment of information prior to marketing of products, with few abilities with respect to the post-marketing period.

For example, Health Canada does not have the ability to require a company to make a label change for a product, to require a company to recall a product, or, if a potential problem is identified, to require a company to provide in-house information or oblige it to conduct another study. As a result, it is usually through non-regulatory means that Health Canada achieves these objectives. However, such an approach is time-consuming, resource-intensive, and means that key information is sometimes not disseminated quickly to those who need it.

The Current System

Looking at Figure 1, which represents the current system of regulating therapeutic products in Canada, the inner circle represents the lifecycle of the product itself. The thick outside lines represent Health Canada's regulatory mandate as regards the product. The lines representing clinical trial reviews, product submissions, and adverse drug reaction reviews are not connected: these activities are managed separately, with lack of information flow among the processes, i.e., lack of a "big picture" approach.

FIG. 1 Current Regulatory Process



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Drivers for Change

The shortcomings of the current point-in-time process have led to a number of drivers for change. There is recognition that "pre-market" datasets have limitations, where patients excluded from clinical trials may be likely candidates for a product once it is on the market; that investigation is lacking in certain patient populations, such as children, pregnant/lactating women, and the elderly; that uncommon or rare adverse events are undetected due to limited study patient populations (once a product is on the general market, the adverse events begin to be seen and although they may be rare, some can be severe, causing the risk/benefit profile to be undesirable or negative for some products; one example is valdecoxib, which was removed from the market due to incidents of Stevens-Johnson Syndrome and other severe skin reactions); and that there is a lack of "real-world" safety and effectiveness data. There are limitations to passive surveillance activities to detect and verify risks, as evidenced by a number of recent high-profile drug withdrawals due to safety concerns. There are modernization efforts in other regulatory jurisdictions, e.g., as regards drugs in pregnancy and lactation, as well as the overall regulation of therapeutic products, particularly in the United States and by the European Medicines Agency (EMA). There has recently been increased scrutiny of regulatory activities, with a focus on openness and transparency, with both the FDA and the EMA issuing consult papers on their policies for openness and transparency. The patterns of disease and product use have changed – Canadians are living longer with chronic conditions, including children. In Canada we have highly educated patient and consumer groups who want to be informed and involved; they demand access to new and promising therapies. Health care practice has evolved; patient-professional partnerships have changed and there are new professional groups. Health Canada's role as a regulator has also changed to being more than just a gatekeeper, but also being an information provider.

International Developments

The Institute of Medicine Report on Drug Safety, released in 2006 after the withdrawal of Vioxx, had a large impact on regulatory activities in both the United States and Canada. The FDA Amendment Act, passed in September 2007, gave the FDA more authority in the post-market environment: enhancing authorities regarding post-market safety of drugs, granting the ability to require post-market studies and clinical trials, to require labelling changes, and to require Risk Evaluation and Mitigation Strategy. Health Canada has been watching the evolution of these changes to see what would be most appropriate to adopt to the Canadian context. The European Union is also at the forefront of regulatory development in this area, with new pharmaceutical legislation introduced in 2004 (both pre- and post-market) and new proposals in 2007, the latter resulting from wide consultations on pharmacovigilance conducted in 2006/2007. The changes include market authorization based on positive benefit/risk balance, the ability to issue conditional market authorizations, and to require risk management systems.

Product Lifecycle

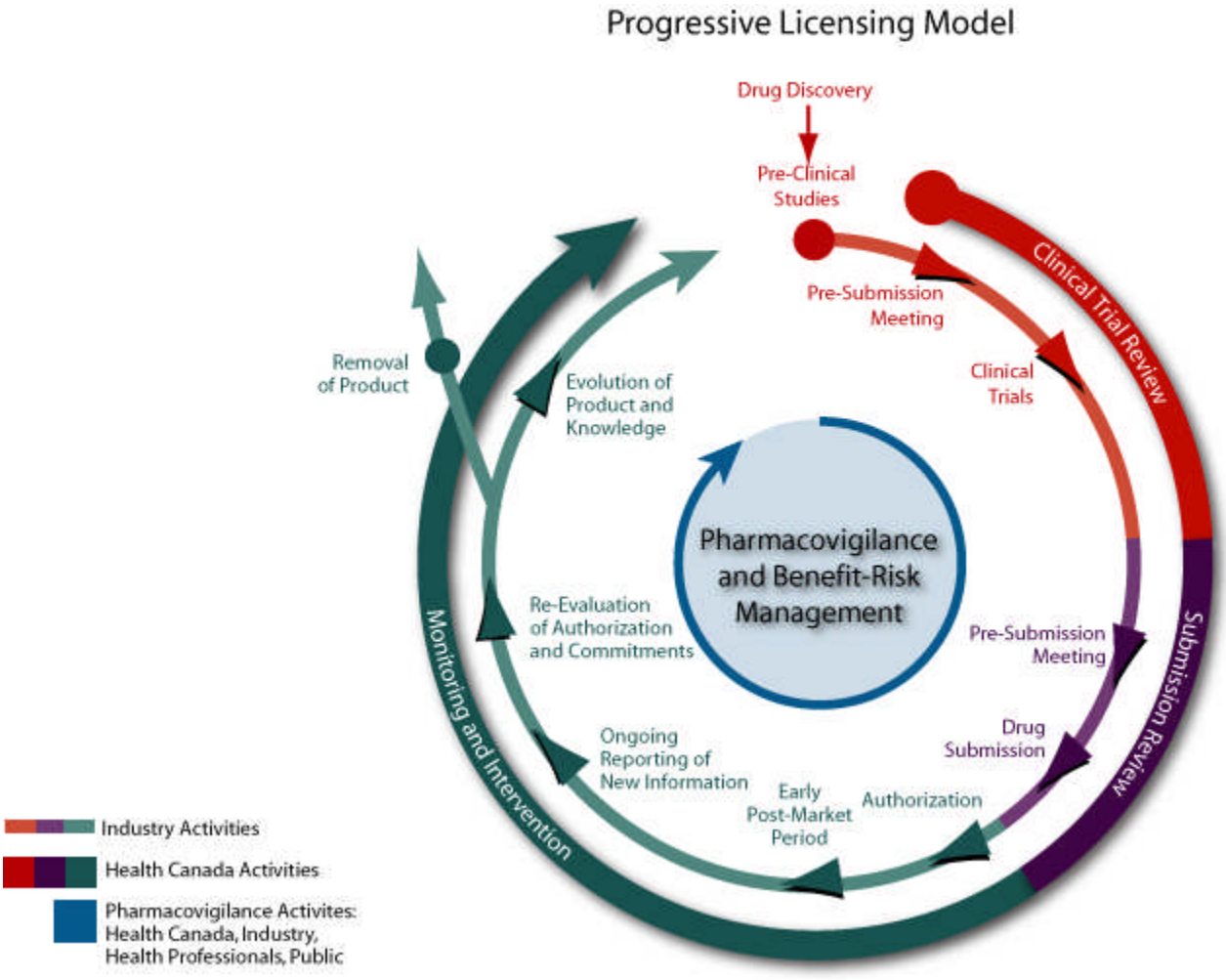
The goal of the product lifecycle project is to develop a modern legislative and regulatory framework that supports access to new therapies; the continuous monitoring, assessment, and communication of product information (benefits and risks) throughout the product lifecycle; and, the optimal use of drugs to maximize benefits and minimize risks. The primary objectives of the framework itself are to protect the public from the marketing of unsafe health products and to support the safest and optimal use of health products.

There are three supporting objectives for the framework:

- To better align the regulatory framework with the systems of health care in Canada to achieve positive health outcomes;
- To 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
- To encourage and make best use of evolutions in the science of drug development and regulation, e.g., incorporation of pharmacogenomic information.

Where Figure 1 showed Health Canada's regulatory activities as being split among a variety of activities, the plan for the lifecycle approach is to have all those activities linked as a continuum (Figure 2). Health Canada would incorporate and make use of the information that continues to develop throughout the lifecycle of a product into a variety of regulatory activities.

FIG. 2 Product Lifecycle Process

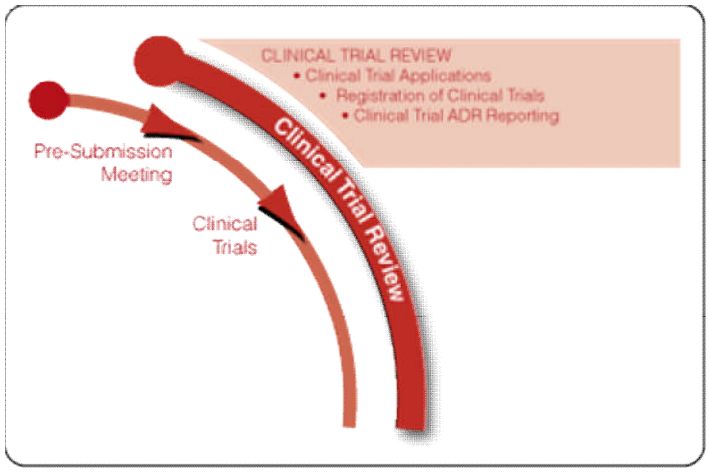


The central concept is that over time there is a progression in knowledge about the benefits and risks of a drug, its use in unique populations—children, pregnant women, the elderly, drug-drug interactions, and new indications. Furthermore, such a process recognizes the limitations of pre-market evaluation and that without a systematic approach; valuable information can be lost. A drug's benefit-risk profile should be evaluated throughout its lifecycle.

Highlights of Lifecycle Activities

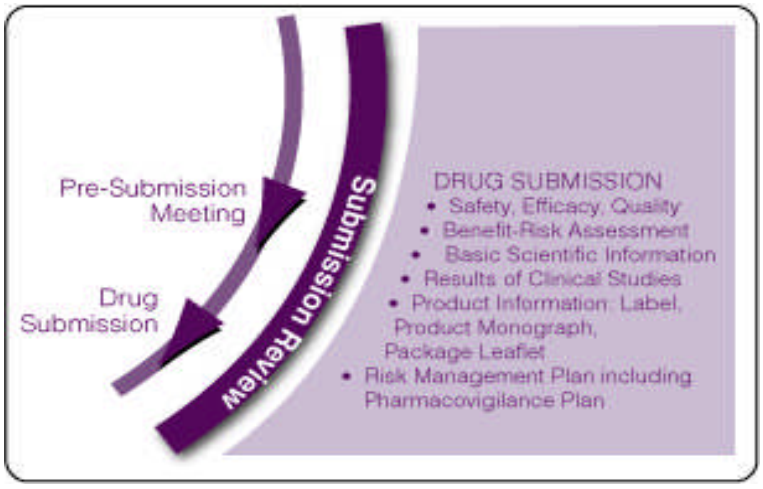
Pre-submission Meetings (Figure 3) would not be required for every product, but a formal meeting procedure would be in place for those who request it. These are useful not only for the clinical trial stage but also at product submission. They could be relied upon and be subject to amendment only where the science underpinning the advice has demonstrably changed.

FIG. 3 Pre-Submission Meetings



Submission Requirements (Figure 4) would vary across product lines and would indicate the information necessary to be submitted for review of the benefit-risk profile. New requirements could include risk management plans, including pharmacovigilance plans.

FIG. 4 Submission Requirements

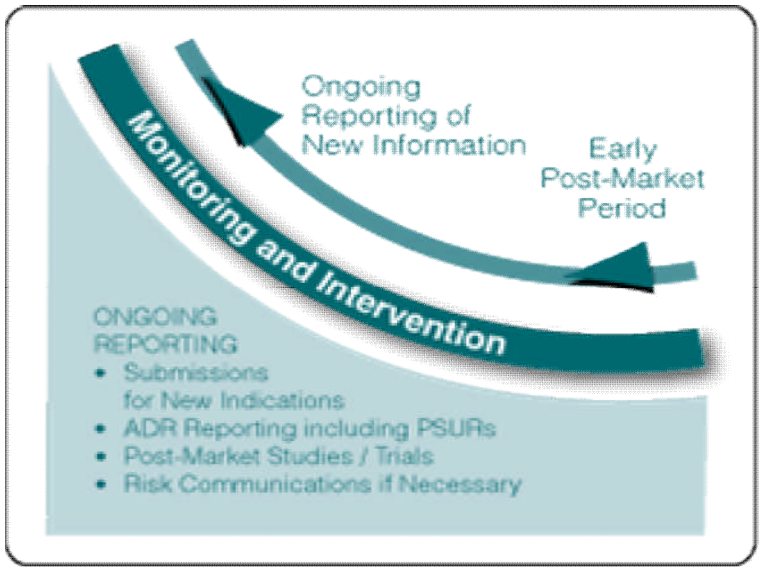


Authorization (Figure 5) would require demonstration of a favourable benefit-risk profile. The favourable benefit-risk profile would need to be maintained throughout the lifecycle of the therapeutic product. The authorization would be capable of requiring ongoing specific obligations of the market authorization holder, i.e., specific terms and conditions set out by Health Canada. Examples could include the identification of specific populations that are to be followed after product approval, such as pregnant and lactating women. Thus, by law, the product sponsor would be required to collect the specified data and submit them to Health Canada. Such information would help to identify whether there is a change to the benefit-to-risk ratio of the product, if information needs to be changed on the product label, and if risk mitigation activities are required for the product.

FIG. 5 Authorization

Post-Authorization (Figure 6), the appropriate regulatory burden would be assessed, based upon the nature and risk of product. There would be obligations for ongoing reporting: filing of safety reports, active surveillance, post-market studies, all of which would be assigned within the authorization. Obligations could be amended, depending upon the benefit-risk profile of the product.

FIG. 6 Post-Authorization



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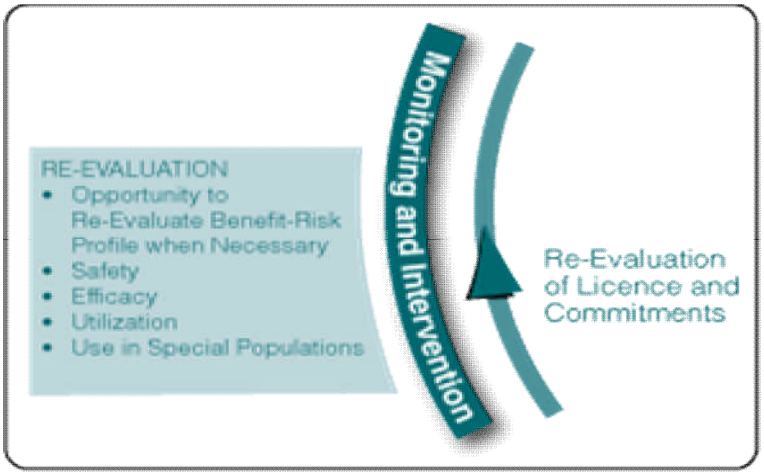
Re-evaluation (Figure 7) would be required where necessary, based upon the risk or nature of the product. The re-evaluation period would be determined according to the product and would be identified as an obligation within the authorization. The extent of re-assessment would similarly be based upon the product and specified within the authorization.

FIG. 7 Re-Evaluation



The Future

With the progressive licensing model (Figure 8), the lifecycle approach, currently implicit, becomes explicit, making expectations clear to both the industry and to Health Canada. The anticipated regulatory framework changes for realization of the model would include:

- Formal incorporation of benefit/risk assessment, in addition to safety, efficacy, quality,
- Ability to authorize products with the requirement for post-market commitments,
- More options for regulation in the post-market period beyond removal of a product, which can leave some patients without a needed therapy,
- Increased emphasis on product information (labels, product monographs, package leaflet); and
- Increased emphasis on evaluation of activities and evaluation of the regulatory framework.

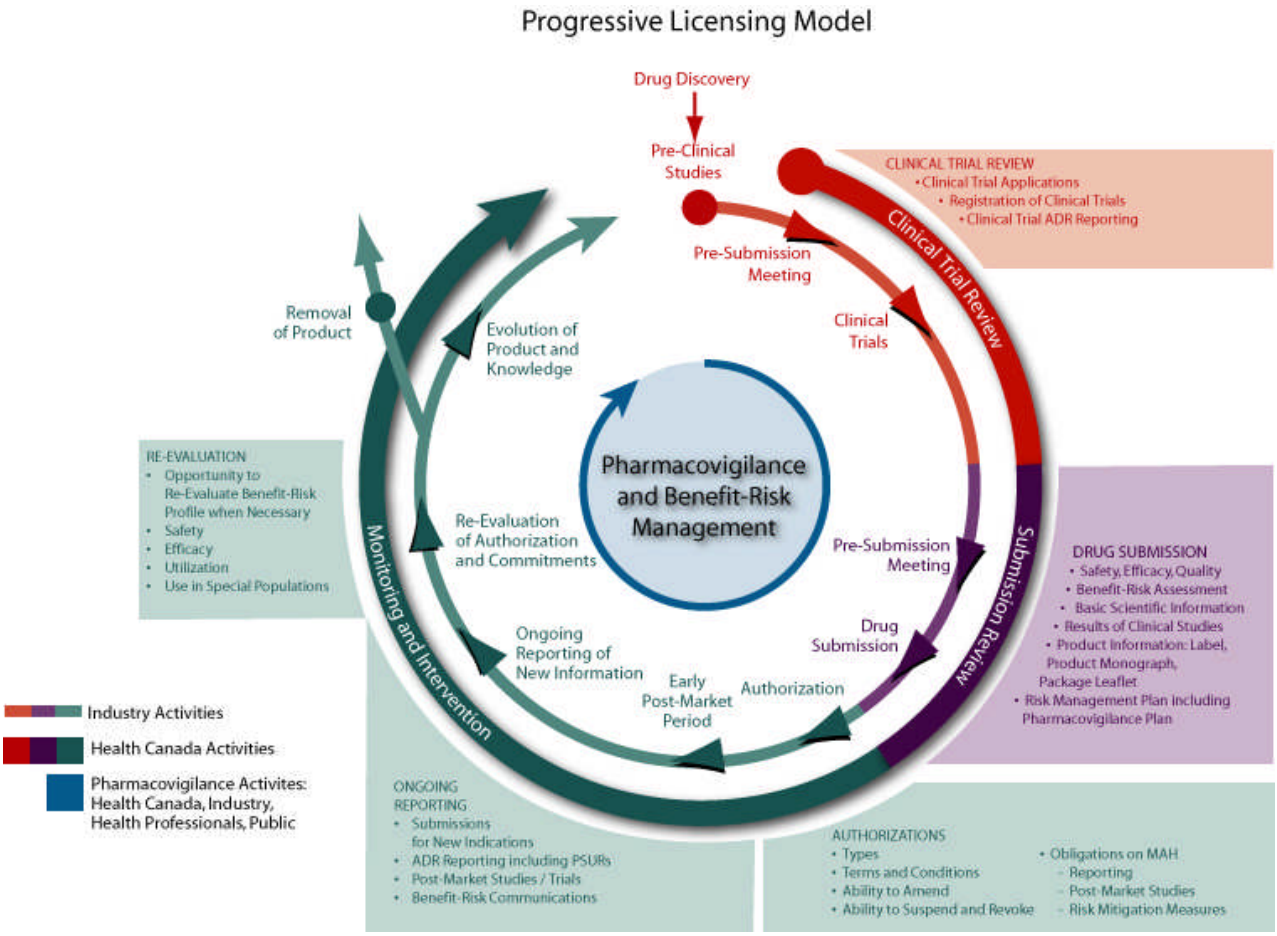
Bill C-51 - An Act to Amend the Food and Drugs Act

On April 8, 2008, Bill C-51 was introduced in the House of Commons. It proposed amendments to the Food and Drugs Act supporting new regulations for health products and food, including:

- Authorization structures with terms and conditions,
- Enhanced post-market surveillance requirements, and
- Modern enforcement and compliance powers.

Bill C-51 expired on the order paper with the dissolution of Parliament in Fall 2008. The intent is to reintroduce proposed legislation—as the reasons for modernization are still valid—with a recommitment stated in the 2010 Speech from the Throne.

FIG. 8 Progressive Licensing Model



Challenges and Opportunities

Drug development is a global enterprise, but regulators need data relevant to their populations. Post-market data are especially important for chronic use drugs. There are special populations—children, the elderly, pregnant and lactating women, those with rare diseases, ethnic groups—that need to be addressed. This could be done through early stage planning by identifying such patients, including them in trials and planning sub-group analyses. How can we better approximate "real-world" use, e.g., concomitant drug use, co-morbidity? Early interaction (in the planning stages) with the regulator is critical, as is work with involved stakeholders, such as highly-motivated patient groups.

What are the appropriate outcome measures for clinical trials and other types of studies? Chronic diseases pose particular challenges. We can learn from professionals and patients as regards the measures they would like to see.

What metrics should we use to evaluate a new regulatory framework? How and what can we learn from other regulators? We need to plan for evaluation of the new regulatory framework itself, so that we can improve upon it over time.

Through our regulatory scheme, we would like to support moving from the beginning of the product lifecycle through to the final removal, without the peaks and valleys that represent the over- and under-treatment of patients, and avoiding exposure in those who should not receive a particular product.

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