

# Building on the Legacy of Vaccines in Canada: Value, Opportunities, and Challenges

## 4

### Pathway to Access: Health Canada Oversight



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Vaccine Industry Committee



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**BIOTECanada**  
Vaccine Industry Committee

# **Pathway to Access: Health Canada Oversight**

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# **La voie de l'accès : La surveillance exercée par Santé Canada**

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## 4.1 Executive Summary / Sommaire

### 4.1.1 Executive Summary

The first key milestone for introducing emerging vaccines into a national immunization program is vaccine licensure (regulatory approval). Thus, overlaid upon the complicated process of developing new vaccine technologies (summarized in Paper 3), stringent regulatory requirements govern procedures for vaccine clinical research, production, and market launch, as described in this paper. At present, the Canadian regulatory environment for new drugs (including complex biologics such as vaccines) is rapidly evolving, particularly as recent advances in medicine and technology underscore the need for a modern regulatory system that can assess novel products in a timely manner – while maximizing patient safety.

Vaccines are highly complex, large-molecule compounds based on living organisms with inherent variability, and hence are more difficult to characterize than traditional pharmaceuticals and other less complex biologics – including therapeutic proteins such as insulin or erythropoietin. Vaccines are also unique in that they are typically administered to large populations of otherwise healthy individuals (including infants and children) to protect against potential future disease. Thus the risk-benefit ratio for vaccines rightly emphasizes the importance of patient safety, and as such, vaccines are held to exacting quality and safety standards, with lower tolerance for adverse events in today's risk-averse society. The resulting strict regulatory oversight of vaccines impacts every step in the production cycle, from initial testing of cell lines to the testing and subsequent surveillance of the final product. As part of this tight regulatory control, increasingly stringent compliance standards have led to higher development costs, as well as greater capital requirements for production facilities – while also lengthening the time-to-market for new vaccine technologies (which may take 15-20 years from initial discovery through to licensure).

The Biologics and Genetic Therapies Directorate (BGTD) is the federal program within Health Canada's Health Products and Food Branch (HPFB) that is responsible for ensuring the safety, efficacy and quality of all biologics, including vaccines for human use. Thus all vaccines authorized for sale in Canada must be reviewed and approved by the BGTD, including careful oversight of preclinical and clinical research programs conducted by vaccine manufacturers. All vaccines produced for human trials in Canada must be manufactured according to internationally recognized Good Manufacturing Practices (GMP). Vaccine developers (sponsors) are required to file a Clinical Trial Application (CTA) for approval by the BGTD prior to initiating clinical trials in Phase I, II and III. In addition, sponsors must conduct all clinical trials – including certain post-licensure trials (e.g. Phase IV studies) that assess long-term vaccine safety and effectiveness – in accordance with the principles of Good Clinical Practices (GCP).

When a manufacturer has generated sufficient scientific and clinical evidence regarding the safety, immunogenicity, efficacy, and quality of a vaccine candidate, an application for licensure known as a New Drug Submission (NDS) is filed with the BGTD. If, after reviewing the NDS, conducting on-site evaluation(s), and completing independent sample testing of at least three lots of vaccine, the BGTD concludes that the benefits of the product outweigh its risks (and any risks can be managed), then the vaccine will be approved for sale in Canada. Within the past few years, reductions in the number of submissions in backlog have been observed, and the BGTD has been successful in meeting its target review time of 300 days for most biologics (including vaccines) and 180 days for those products that meet the criteria for priority review status.

Following regulatory approval, Health Canada continues to monitor the safety and effectiveness of vaccines on an ongoing basis, e.g. through stringent post-market surveillance and lot release programs. Other key elements of the post-licensure regulation of vaccines include Health Canada oversight of post-market changes, as well as inspection and enforcement activities. Overall, with this level of pre- and post-licensure regulation, vaccines used in Canada are highly effective and safe, and have demonstrated excellent value in terms of protecting public health and contributing to the greater “public good”.

As many new drugs (including vaccines) are expected to be submitted for review by Health Canada within the next few years, it is essential that Canada's regulatory review process undergoes appropriate modernization to reflect evolving science, values and practices across the country's dynamic health care landscape. With the publishing of its *Blueprint for Regulatory Renewal* in October 2006, and the subsequent tabling of Bill C-51 in April 2008 as the legal groundwork for regulatory modernization within this context, Health Canada has recently taken on the challenge of modernizing Canada's regulatory system for health products for the first time in 40 years.

As one major initiative under the recently proposed *Blueprint*, Health Canada is modernizing the regulatory process for drugs through a project called the Progressive Licensing Framework (PLF) – currently referred to under the auspices of “Legislative and Regulatory Modernization” – which is intended to provide a mechanism for the continuous monitoring and reassessment of a drug's safety, quality and effectiveness throughout its life cycle. It is currently anticipated that draft PLF documents will be released following the introduction of a revised Bill C-51, i.e. by late 2009. As of July 2009, many issues remain unresolved, and the industry awaits further clarification regarding specific procedures and practices (e.g. for individual drugs or product classes) to be introduced under the PLF.

As another element of recent modernization efforts, Health Canada has undertaken an independent evaluation process to specifically review the current regulatory framework for vaccines, beginning in 2006. The initial phase of this project revealed several weaknesses, including the current “patchwork” of outdated product-specific and general regulations, and the lack of vaccine-specific guidance documents – particularly in light of modern vaccine technology and manufacturing processes. In addition, there was strong consensus regarding the need for harmonization of regulatory policies that govern vaccine use with international standards and best practices, i.e. to help reduce overall vaccine development costs, to minimize delays in regulatory approvals, and to stimulate investment in future research. As of July 2009, relevant stakeholders are still awaiting further communication from Health Canada regarding recent progress and the current status of the modernization project for vaccine regulation in Canada.

Yet another imminent challenge on the regulatory horizon will be to determine how the emerging class of therapeutic vaccines (which are intended to treat existing disease, rather than provide prophylactic protection) will be regulated by Health Canada. Based on current international models, it appears likely that therapeutic vaccines will be regulated as other biologics by the BGTD. However, agreement on definitions and potential sub-classes of therapeutic vaccines is still urgently required – especially given the fast pace of technology advancement.

Overall, significant work lies ahead in terms of modernizing Canada's regulatory system for health products, including biologics such as vaccines. Close coordination across many individual processes – including the re-drafting of Bill C-51, advancement of the PLF and the vaccine regulatory framework, and continued development of guidelines and/or regulations pertaining to emerging therapeutic vaccines and subsequent entry biologics (SEBs) – will be critical in the context of Canada's broader modernization mandate. As proposed amendments are further debated and finalized, it is critical that decision-makers recognize the unique, complex characteristics of vaccines, and maintain open dialogue in working towards regulatory policies that ultimately support timely patient access and efficient immunization program implementation. To this end, BIOTECanada's Vaccine Industry Committee (VIC) has put forward the following recommendations for consideration by federal/provincial/territorial (F/P/T) governments and other key stakeholders.

### Federal/Provincial/Territorial Recommendations

1. To maximize the medical, social and economic benefits of vaccines for all Canadians, regulatory policies should, at all levels, aim to remove any procedural barriers to the rapid adoption of new immunization programs in Canada, including the development of less duplicative (national) regulatory licensure and (F/P/T) evaluation/recommendation procedures (see Paper 5).
2. In finalizing and implementing its proposed progressive licensing framework (PLF) as a key element of the revised Bill C-51, Health Canada should provide well-defined guidelines that address a life cycle approach that is relevant to the individual drug (or vaccine) and its specific benefit-risk profile – rather than to mandate a single, rigid life cycle approach across all products.
3. With regard to modernizing the regulatory framework for vaccines, Health Canada should develop forward-looking regulations and vaccine-specific guidance documents that reflect the rapid advancement in vaccine technology, clinical research and manufacturing processes, e.g. including: i) the development of combination, therapeutic and/or cancer vaccines; ii) future use of biomarkers as surrogate endpoints for vaccine efficacy; and iii) modern process validation and lot testing methods.
4. With respect to emerging therapeutic vaccines, Health Canada should provide early opportunities for collaborative, transparent discussions with vaccine manufacturers regarding appropriate definitions and mechanisms to guide their regulation, ideally in close alignment with international standards.
5. In general, Health Canada's regulatory policies that govern vaccine use should be harmonized with international (ICH) regulatory standards, and aligned where possible with best practices of leading regulatory agencies worldwide (e.g. in the United States and European Union).

### Stakeholder Recommendations

6. Stakeholders at all levels, including F/P/T government officials, regulatory and public health authorities, vaccine manufacturers, academic researchers, health care professionals, and the general public should actively engage in transparent dialogue, thus supporting vaccine manufacturers in meeting the strict (and rapidly evolving) regulatory requirements of Health Canada, while also satisfying increasing patient demands in terms of understanding vaccine safety and effectiveness.

## 4.1.2 Sommaire

*La première étape importante de l'intégration de nouveaux vaccins à un programme national d'immunisation est leur homologation (approbation réglementaire). Ainsi, outre le processus complexe qu'est le développement de nouvelles technologies vaccinales (dont un résumé est présenté dans le document 3), les procédures relatives à la recherche clinique sur les vaccins, à leur fabrication et à leur lancement sur le marché sont assujetties à des exigences réglementaires rigoureuses, comme l'explique le présent document. La réglementation canadienne relative aux nouveaux médicaments (y compris les produits biologiques complexes comme les vaccins) connaît une évolution rapide, en raison notamment du fait que les récentes percées médicales et technologiques soulignent la nécessité de mettre en place un système de réglementation moderne, capable d'évaluer les nouveaux produits en temps opportun, tout en maximisant la sécurité des patients.*

*Les vaccins sont des composés très complexes à grandes molécules, provenant d'organismes vivants dotés d'une variabilité propre. Ils sont donc plus difficiles à caractériser que les produits pharmaceutiques traditionnels et d'autres produits biologiques moins complexes, y compris les protéines thérapeutiques comme l'insuline et l'érythropoïétine. Les vaccins sont aussi des produits uniques en ce sens qu'on les administre habituellement à de vastes populations en bonne santé (y compris les bébés et les enfants) afin de les protéger contre d'éventuelles maladies. Ainsi le rapport risques-avantages des vaccins souligne-t-il à juste titre l'importance de la sécurité des patients. Les vaccins sont donc assujettis à des normes de qualité et d'innocuité, le degré de tolérance vis-à-vis des effets indésirables étant plus faible au sein de la société d'aujourd'hui, peu encline à prendre des risques. Il en résulte une surveillance réglementaire rigoureuse ayant une incidence sur toutes les étapes de leur fabrication, allant des premières analyses des lignées cellulaires aux essais et à la surveillance subséquente du produit final. Cette surveillance étroite du respect de normes de plus en plus rigoureuses a donné lieu à une augmentation des coûts de développement, ainsi que des besoins en capitaux nécessaires au financement des installations de production, et allongé les délais de commercialisation des nouvelles technologies vaccinales (il peut s'écouler de 15 à 20 ans entre la découverte initiale du produit et son homologation).*

*La Direction des produits biologiques et des thérapies génétiques (DPBTG), dont est notamment composée la Direction générale des produits de santé et des aliments (DGPSA) de Santé Canada, est l'autorité fédérale chargée d'assurer l'innocuité, l'efficacité et la qualité de tous les produits biologiques, y compris les vaccins d'usage humain. Ainsi, tous les vaccins dont la vente est autorisée au Canada doivent être évalués et approuvés par le DPBTG, qui exerce également une surveillance étroite des programmes de recherche préclinique et clinique menés par les fabricants. Tous les vaccins d'usage humain destinés à des essais cliniques au Canada doivent être conformes aux bonnes pratiques de fabrication (BPF) reconnues à l'échelle internationale. Les entreprises qui développent les vaccins (promoteurs) sont tenues de présenter une Demande d'essai clinique (DEC) à la DPBTG aux fins d'approbation avant d'entreprendre des essais cliniques de phase I, II et III. Les promoteurs doivent également mener tous les essais cliniques, y compris certains essais post-homologation (de phase IV, par exemple) visant à évaluer l'innocuité et l'efficacité à long terme des vaccins, conformément aux bonnes pratiques cliniques (BPC).*

*Après que le fabricant a fourni des preuves scientifiques et cliniques suffisantes de l'innocuité, de l'immunogénicité, de l'efficacité et de la qualité du candidat-vaccin, il doit déposer une demande d'homologation appelée Présentation de drogue nouvelle (PDN) auprès de la DPBTG. Si la DPBTG, après avoir examiné la PDN, mené des évaluations sur place et réalisé des tests indépendants à l'aide d'échantillons d'au moins trois lots de vaccins, déduit que le produit présente plus d'avantages que de risques (et que ces risques peuvent être gérés), elle en approuvera donc la vente au Canada. On constate, depuis les dernières années, une réduction du nombre de présentations en souffrance. La DPBTG est également parvenue à respecter le délai d'examen de 300 jours qu'elle s'était fixé pour la plupart des produits biologiques, y compris les vaccins, et de 180 jours pour les produits exigeant un examen prioritaire.*

*Au terme de l'approbation réglementaire, Santé Canada continue de surveiller l'innocuité et l'efficacité des vaccins régulièrement, notamment dans le cadre de programmes rigoureux de surveillance post-commercialisation et d'autorisation de mise en circulation d'un lot. Outre la réglementation des vaccins après leur homologation, Santé Canada exerce également une surveillance des changements apportés après la commercialisation et tient des activités d'inspection et d'application de la loi. En général, grâce aux mécanismes rigoureux de réglementation qui sont mis en place avant et après leur homologation, les vaccins utilisés au Canada sont très efficaces et sécuritaires, et constituent une excellente valeur pour ce qui est de protéger la santé publique et de contribuer au « bien commun ».*

*Comme on prévoit que beaucoup de nouveaux médicaments, y compris des vaccins, feront l'objet d'une présentation à Santé Canada aux fins d'examen au cours des prochaines années, il est essentiel que le processus canadien d'examen réglementaire soit modernisé comme il se doit pour qu'il tienne compte des connaissances scientifiques, des valeurs et des pratiques nouvelles qui composent le système dynamique des soins de santé au Canada. Avec la publication de son Plan de renouveau en octobre 2006 et le dépôt subséquent du projet de loi C-51 en avril 2008, qui constitue les fondements juridiques d'une modernisation de la réglementation dans ce contexte, Santé Canada a, pour la première fois en 40 ans, relevé le défi de moderniser le système canadien de réglementation des produits de santé.*

*Parmi les principales initiatives énoncées dans son récent Plan de renouveau, Santé Canada a entrepris de moderniser le processus de réglementation des médicaments dans le cadre d'un projet appelé Cadre d'homologation progressive (CHP) – désigné actuellement sous l'appellation « modernisation des lois et des règlements », – destiné à mettre en place un mécanisme de surveillance et de réévaluation continues de l'innocuité, de la qualité et de l'efficacité d'un médicament durant tout son cycle de vie. On prévoit que les documents provisoires du CHP seront publiés à la suite du dépôt d'une version révisée du projet de loi C-51, c'est-à-dire vers la fin de 2009. En date de juillet 2009, de nombreuses questions demeuraient sans réponse, et l'industrie attendait d'autres précisions concernant les procédures et pratiques particulières (se rapportant, par exemple, à chaque médicament ou catégorie de médicaments) qui seront adoptées dans le cadre du projet d'homologation progressive.*

*Dans le cadre de ses récents efforts de modernisation, Santé Canada a amorcé en 2006 un processus d'évaluation indépendante visant notamment le système actuel de réglementation des vaccins. L'étape initiale du projet a révélé diverses lacunes, y compris l'actuelle « courtepointe en patchwork », ensemble désuet de règlements généraux et particuliers se rapportant aux produits, et l'absence de documents d'orientation propres aux vaccins, qui tiennent compte notamment des nouvelles technologies vaccinales et méthodes de fabrication. Tous les intervenants ont également souligné la nécessité d'harmoniser les politiques de réglementation régissant l'utilisation des vaccins avec les normes et pratiques exemplaires internationales en vue, notamment, de réduire les coûts généraux associés au développement des vaccins, de minimiser les délais d'approbation réglementaire et de stimuler les investissements dans de prochains travaux de recherche. En date de juillet 2009, les intervenants concernés attendaient encore d'autres renseignements de la part de Santé Canada concernant les progrès récents et l'état actuel du projet de modernisation de la réglementation des vaccins au Canada.*

*Encore un autre défi se pointe à l'horizon au chapitre de la réglementation. Il s'agira, en effet, de déterminer comment Santé Canada réglera la nouvelle catégorie de vaccins thérapeutiques (qui visent à combattre des maladies existantes plutôt qu'à conférer une protection prophylactique). D'après les modèles internationaux actuels, il semble probable que les vaccins thérapeutiques seront réglementés par la DPBTG au même titre que d'autres produits biologiques. Cependant, il demeure urgent d'arriver à un accord quant aux définitions et aux sous-catégories possibles des vaccins thérapeutiques, compte tenu, notamment, du rythme rapide des progrès technologiques.*

En général, la modernisation du système canadien de réglementation des produits de santé, y compris les produits biologiques comme les vaccins, représente un défi de taille. Une coordination efficace de nombreuses initiatives (dont le remaniement du projet de loi C-51, la promotion du CHP et du cadre de réglementation des vaccins, ainsi que l'élaboration continue de lignes directrices et/ou de règlements concernant les nouveaux vaccins thérapeutiques et produits biologiques ultérieurs) sera primordiale dans le cadre du mandat élargi du Canada en matière de modernisation. Alors que des projets de modifications sont débattus de nouveau et peaufinés, il est essentiel que les décideurs reconnaissent le caractère unique et complexe des vaccins, et continuent de dialoguer ouvertement en vue d'adopter des politiques de réglementation qui, en bout de ligne, favoriseront l'accès des patients en temps opportun et la mise en œuvre efficace des programmes d'immunisation. À cette fin, le Comité de l'industrie des vaccins (CIV) de BIOTECanada a formulé les recommandations suivantes à l'intention des gouvernements fédéral, provinciaux et territoriaux, et d'autres intervenants clés.

### Recommandations à l'intention des gouvernements fédéral, provinciaux et territoriaux

1. Pour que tous les Canadiens tirent le maximum des avantages médicaux, sociaux et économiques des vaccins, les gouvernements de tous les paliers doivent adopter des politiques de réglementation visant à supprimer les barrières administratives qui entravent la mise en œuvre rapide de nouveaux programmes d'immunisation au Canada, et élaborer un processus national d'homologation réglementaire et un processus fédéral, provincial et territorial d'évaluation et de recommandation qui limitent le chevauchement des tâches (voir le document 5).
2. Afin de peaufiner et de mettre en œuvre son projet de cadre d'homologation progressive (CHP), élément important de la version révisée du projet de loi C-51, Santé Canada doit présenter des lignes directrices bien définies, prônant l'adoption d'une approche de réglementation qui reconnaît le cycle de vie de chaque médicament ou vaccin et son profil risques-avantages, plutôt qu'une approche unique et stricte, qui englobe tous les produits.
3. En ce qui a trait à la modernisation du cadre de réglementation des vaccins, Santé Canada doit élaborer des règlements de nature prospective et des documents d'orientation propres aux vaccins, qui tiennent compte de l'évolution rapide des technologies vaccinales, de la recherche clinique et des procédés de fabrication, y compris notamment i) le développement de vaccins combinés, thérapeutiques et/ou anticancéreux; ii) l'utilisation future de biomarqueurs comme critères de substitution pour mesurer l'efficacité d'un vaccin; et iii) l'adoption de méthodes modernes de validation de processus et de mise à l'essai de lots.
4. Concernant les nouveaux vaccins thérapeutiques, Santé Canada doit, dès que possible, cibler des occasions d'engager des discussions concertées et transparentes avec les fabricants de vaccins afin d'élaborer des définitions et mécanismes adéquats, qui orienteront la réglementation des vaccins, idéalement dans le respect des normes internationales.
5. En général, les politiques de réglementation de Santé Canada qui régissent l'utilisation des vaccins doivent s'harmoniser aux normes internationales de réglementation (CIH) et être conformes, dans la mesure du possible, aux pratiques exemplaires des principaux organismes de réglementation dans le monde (p. ex., aux États-Unis et dans les pays de l'Union européenne).

### Recommandations à l'intention d'autres intervenants

6. Tous les intervenants, y compris les représentants des gouvernements fédéral, provinciaux et territoriaux, les autorités en matière de réglementation et de santé publique, les fabricants de vaccins, les chercheurs universitaires, les professionnels de la santé et le grand public, doivent s'engager activement à tenir un dialogue transparent pour ainsi aider les fabricants de vaccins à satisfaire aux exigences réglementaires rigoureuses de Santé Canada (qui connaissent une évolution rapide), tout en répondant aux exigences croissantes des patients, qui souhaitent obtenir une compréhension accrue concernant l'innocuité et de l'efficacité des vaccins.

## 4.2 Stringent Regulatory Oversight of Vaccines

In formulating and executing a comprehensive plan for introducing new vaccines into a national immunization program, the first key milestone for vaccine adoption in every country is vaccine licensure (regulatory approval). Thus, overlaid upon the complicated process of developing new vaccine technologies (Paper 3), stringent regulatory requirements govern vaccine clinical research, production, market launch and distribution processes. In Canada and other developed countries, vaccine licensure is followed by the development of national recommendations to guide the adoption of immunization programs (Paper 5). Subsequently, the implementation of appropriate vaccine financing mechanisms – as well as large-scale manufacturing, education and delivery programs – are critical elements in supporting successful vaccine uptake and hence the commercial viability of vaccine innovations (Papers 6, 7, and 8).

Unlike traditional pharmaceuticals, vaccines are biological products based on living organisms with inherent variability, and the exact molecular elements that provide protection are not always wholly understood.<sup>1</sup> In addition, the active compounds of vaccines are significantly greater in size than typical small-molecule pharma drug entities. As just one example, the virus-like particle (VLP) used as the basis for the human papillomavirus (HPV) vaccine is more than 10,000-fold larger than a typical small-molecule drug, and its dose is specified as a function of both its weight and biological potency (rather than by weight alone). In view of the substantial challenges associated with the analytical characterization of vaccines, there has been a historic tendency in vaccine development to define the product mainly via its production process.<sup>2</sup> Overall, since vaccines are highly complex substances that are much more difficult to characterize than many pharmaceuticals, more stringent regulatory oversight is required for vaccines than for traditional pharma drugs – or indeed compared to other biologics, including therapeutic proteins such as insulin or erythropoietin, for which analytical characterization is relatively less difficult.

In contrast to most drugs, biologically-based vaccines (including killed, inactivated; live, attenuated; and other classes) can also be compromised during the manufacturing process. Hence quality control, aseptic processes and monitoring have become non-negotiable for vaccine production. Even with strict regulatory standards, however, the possibility of contamination remains (although this risk is much lower today than several decades ago). In addition, clinical development of vaccines must be closely monitored to ensure that a vaccine candidate does not elicit unwanted serious side effects, but rather demonstrates appropriate safety and efficacy in the context of the disease or infection it aims to prevent or treat. Furthermore, since even slight variations in the production process may give rise to different biological properties, any changes in manufacturing process or scale require reassurance that the product will remain unchanged in terms of its safety and efficacy, and satisfactory proof will be demanded by regulatory authorities.

Another important distinction between developing vaccines and most other therapeutic medicines is that vaccines are typically administered to large populations of otherwise healthy individuals (including infants and children) to protect against potential future disease, rather than to treat individuals suffering from disease. Thus the risk-benefit ratio for vaccines rightly emphasizes the importance of patient safety, and as such, vaccines are held to exacting quality and safety standards (with lower tolerance for adverse events) in today's risk-averse society.<sup>3</sup> The resulting strict regulatory oversight impacts every step in the production cycle, from initial testing of cell lines to the testing of the final vaccine product. As part of this tight regulatory control, all vaccine manufacturing procedures must be described and characterized in great detail, including the nature and performance of the specific equipment used for every step of the production process.

Given the complexity of modern vaccine technologies, as well as the need for specialized manufacturing facilities, one of the greatest hurdles in vaccine development is translating basic science into real vaccines that can be produced in compliance with demanding regulatory requirements on a sufficient scale to have a meaningful public health impact. For vaccines with wide utility, the ability to consistently manufacture tens of millions of doses per year is required; the broad quality goal is that each and every dose is equivalent, safe and effective. Taking this perspective, the regulatory burden can be described as the level of proof and documentation necessary to provide assurance that this broad quality goal is achieved on an ongoing basis.

Overall, increasingly stringent regulatory compliance standards have led to higher vaccine development costs, as well as greater capital investment requirements for manufacturing facilities – while also lengthening the time-to-market approval of new vaccine technologies (which may take 15-20 years from initial discovery through to licensure).<sup>4</sup> Another significant challenge in vaccine development includes meeting the stringent regulatory requirements of health authorities while satisfying increasing patient demands in terms of understanding vaccine safety and quality,<sup>5</sup> i.e. to help overcome resistance to vaccine acceptance – as part of the “anti-vaccine movement” (see Paper 8). Within the broader context of evolving regulatory compliance requirements to help protect patient safety, it should be noted that Canada is developing a system for introducing vaccine bar codes in compliance with global standards (see Paper 9).

## 4.3 Current Regulation of Vaccines in Canada

### 4.3.1 Health Canada's Biologics and Genetic Therapies Directorate (BGTD)

Like all medicines, vaccines must undergo rigorous review and testing before they are licensed for commercial use. In Canada, biologic drugs are regulated by the *Food and Drugs Act* and the *Food and Drug Regulations*. The Biologics and Genetic Therapies Directorate (BGTD) – which falls under the purview of Health Canada's Health Products and Food Branch (HPFB) – is the federal regulatory authority that is responsible for ensuring the safety, efficacy and quality of all biologics, including vaccines for human use in Canada.<sup>6</sup> Thus all vaccines authorized for sale in Canada must be reviewed and approved by the BGTD. Health Canada also regulates all aspects of vaccine production by manufacturers, to ensure safety, sterility, and quality of large-scale batches or “lots”.<sup>7</sup> Once a vaccine has been approved by Health Canada's BGTD, it is then subject to the scrutiny of the National Advisory Committee on Immunization (NACI) under the auspices of the Public Health Agency of Canada (PHAC), the national expert body that provides scientific recommendations for immunization programs in Canada (refer to Paper 5).

### 4.3.2 Pathway to Market Licensure

As introduced in Paper 3, if a promising vaccine candidate emerges from discovery research – with demonstration of suitable purity, safety, potency, immunogenicity and protectiveness in animal models – clinical trials are then conducted in human subjects to test the safety and efficacy of the potential vaccine. Scientific evidence from both preclinical and clinical studies will be used to eventually support the submission dossier for regulatory approval in Canada, as compiled by various departments of vaccine manufacturers, including discovery, clinical development and regulatory affairs teams. The key phases of clinical research, which mirror the structure of pre-market clinical research for traditional pharmaceutical compounds, are described briefly below.<sup>8,9,10</sup>

All vaccines produced for human trials in Canada must be manufactured according to internationally recognized Good Manufacturing Practices (GMP). Vaccine developers (study sponsors) are required to file a Clinical Trial Application (CTA) for approval by Health Canada's BGTD prior to initiating clinical trials in Phase I, II and III. A CTA is also required for certain post-licensure (e.g. Phase IV) trials involving marketed vaccines, particularly where the investigation is to be conducted outside the parameters of the authorized Notice of Compliance (NOC) or Drug Identification Number (DIN) application.<sup>11</sup> Sponsors must conduct all clinical trials, including Phase IV trials, in accordance with the principles of Good Clinical Practices (GCP), e.g. incorporating the essential elements of informed consent of research subjects and Research Ethics Board (REB) approval.

**Phase I** – Phase I trials are typically limited to a small number of healthy participants (20 to 100) and are frequently initiated in healthy adults and then move to groups likely to be the target populations for the vaccine, such as young children. The primary goal of these trials is to gather preliminary data on the safety of the vaccine (including evaluation of potential side effects such as local/systemic reactions) and its ability to trigger an immune response. Vaccine candidates that elicit an immune response are deemed to be immunogenic. Phase I trials may also be designed to examine different doses of the vaccine to aid the selection of the optimal dose for evaluation in subsequent phases of clinical development. A Phase I trial usually takes eight to 12 months to complete.

**Phase II** – Phase II trials involve a larger number of healthy subjects (often several hundred), and are often divided into two broad categories. Phase IIa studies seek to validate the preliminary data regarding safety and immunogenicity generated in Phase I trials. Phase IIb studies can be used to obtain more precise data on the magnitude of immune response as it relates to dosage and dose intervals, and may also focus on the populations for whom the vaccine is likely to be recommended. Phase II trials generally take 18-24 months; the increase over Phase I is due primarily to the additional time required for screening and enrolling larger numbers of trial participants.

**Phase III** – Phase III trials are large, randomized (often double-blind and placebo-controlled) studies that may enroll (for certain vaccines) tens of thousands of healthy individuals. These pivotal studies validate the safety and efficacy (or immunogenicity) data generated through Phases I and II in a much larger and more diverse segment of the overall population. Phase III studies may also measure vaccine efficacy and safety among vaccine recipients relative to a control group, usually placebo recipients. These studies generally seek to demonstrate that incidence of the relevant disease is significantly lower in vaccine recipients than in placebo recipients, and thus long-term observation of study participants is required (often for several years post-vaccination) to determine whether the immune response triggered by the vaccine actually confers disease protection. Phase III trials of vaccines are generally expected to require a minimum of two to three years for subject enrollment, immunizations, and follow-up assessment of efficacy. In this context, it should be noted that vaccine efficacy is assessed in subjects enrolled in clinical trials, while *effectiveness* refers to efficacy assessed across a broader population, i.e. once a vaccination program has been established for some time.

When a manufacturer has generated sufficient scientific and clinical evidence regarding the safety, immunogenicity, efficacy, and quality of a vaccine candidate, an application for licensure known as a New Drug Submission (NDS) is filed with the BGTD. The submission must also include detailed information regarding manufacturing and testing methods, and the production facility. Manufacturers also provide a Product Monograph that summarizes clinical indications, dosage, product characteristics and storage, and all important safety and efficacy recommendations to help optimize product utilization (including potential drug interactions and concomitant administration). Prior to market authorization, the vaccine manufacturer is subjected to an on-site evaluation coordinated by members of the BGTD in conjunction with the Health Products and Food Branch Inspectorate (HPFBI), i.e. to assess the quality of the production process and to determine that the manufacturer is able to conduct the necessary quality controls in compliance with current GMP (cGMP). The manufacturer must also provide samples of at least three (and preferably five) lots of the vaccine for testing at BGTD laboratories.

If, after completing the review of the NDS, the on-site evaluation(s), and the independent laboratory testing of samples, the conclusion is that the benefits of the product outweigh its risks (and any risks can be managed), then the vaccine is issued an NOC and a DIN indicating that it is authorized for sale in Canada. Conversely, if there is insufficient evidence to support safety, efficacy or quality claims, the BGTD will not issue an NOC or DIN for the vaccine, and the product cannot be sold in Canada. Similarly stringent requirements and procedures are in place for market authorization by other regulatory bodies, such as such as the Center for Biologics Evaluation and Research (CBER) of the United States Food and Drug Administration (FDA)<sup>12,13</sup> or the European Medicines Agency (EMA).<sup>14</sup> In this context, it should be noted that new vaccines can be licensed without prior clinical studies conducted in Canada if BGTD reviewers believe that the data generated elsewhere, such as in the United States (U.S.) or European Union (E.U.), apply domestically.<sup>15</sup>

With regard to timelines, completion of Phase I, II, and III clinical trials may require six to 10 years (or possibly longer), depending upon the time required for protocol development, subject enrollment, data collection and analyses, as well as regulatory submission and approval at each successive stage. Until very recently, the regulatory process to review/approve the NDS after completion of Phase III trials (i.e. the time elapsed from submitting the registration file to receipt of NOC) had been taking approximately one to two additional years in Canada for most vaccines.<sup>16,17</sup> However, within the past two years,<sup>18</sup> Health Canada's BGTD has successfully been meeting its target review time of 300 days for most biologics (including vaccines), and 180 days for those products that meet the criteria for priority review status.<sup>i</sup> Recent reductions in the number of submissions in backlog have helped to facilitate hitting these performance targets for emerging vaccines.<sup>19</sup> It is noteworthy that Merck's HPV vaccine, Gardasil, was granted priority review status by the BGTD (as well as by the FDA and the EMEA), and was approved in Canada within the 180 day target timeframe in July 2006.<sup>20</sup>

### 4.3.3 Post-Market Regulation

Following regulatory approval, post-licensure trials are often performed to assess long-term vaccine effectiveness, as well as the health, social and economic effects of the vaccine (e.g. under "real world" conditions).<sup>21</sup> In addition, post-licensure vaccine safety is evaluated through multiple means. Specifically, after any vaccine receives marketing approval in Canada, voluntary and mandatory post-market surveillance and adverse event reporting occur, as described in Paper 9. Vaccine manufacturers are required by law to report to Health Canada any serious adverse events related to immunization within 15 days of notification of their occurrence,<sup>22</sup> and manufacturers must also provide periodic safety update reports (PSURs) – which summarize adverse reactions – as requested by Health Canada.<sup>23</sup>

In overseeing Canada's national vaccine surveillance systems, the PHAC coordinates and supports the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS), a passive surveillance system which collects reports from health care providers on adverse events following immunization. Canada also has an active surveillance system, called the Immunization Monitoring Program ACTive (IMPACT) system, for documenting adverse events following immunization through 12 pediatric hospitals across the country.<sup>24</sup> The goal of this national vaccine safety surveillance is to monitor vaccines used in Canada and to detect, as quickly as possible, any evidence or concern regarding safety. If unexpected or increased side effects due to vaccines occur, the BGTD and PHAC decide upon the best course of action for resolution.

In addition to vaccine monitoring via post-market surveillance, all vaccines sold in Canada (as in other jurisdictions) undergo ongoing lot release evaluation even after they have been approved. To support this process, vaccines are placed on a lot release schedule tailored to their potential risk.<sup>25</sup> In the majority of cases, for each lot of vaccine to be sold in Canada, the manufacturer must continue to submit the results of (and protocols for) its own testing, in addition to providing lot samples for independent evaluation by the BGTD. In order to sell new lots of the vaccine, manufacturers must demonstrate that each new lot is the same in its specific characteristics (e.g. purity, sterility, pH, etc.) as the lots tested prior to market authorization, i.e. before release to the market for distribution. This method allows experts to reasonably determine that the new vaccine lots are as safe and effective as previous lots. Each new lot must also meet the criteria approved by Health Canada for market authorization; these criteria may change due to test or production variations. If a vaccine lot meets all required specifications, a formal release letter is issued to approve the sale of that particular lot in Canada.<sup>26</sup> Manufacturers of biologic products, including vaccines, are also required to submit a Yearly Biologic Product Report (YBPR); this annual report is used to assess the ongoing safety and quality of the vaccine, i.e. to verify the consistency of the process and to identify potential trends. The lot release

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<sup>i</sup> According to Health Canada, priority review status applies to NDS submissions for a serious, life-threatening or severely debilitating disease or condition for which there is substantial evidence of clinical effectiveness that the drug provides: i) effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada; or ii) a significant increase in efficacy and/or significant decrease in risk such that the overall benefit/risk profile is improved over existing therapies, preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada. Source: Administrative Corrections to Health Canada's Priority Review Documents, Health Canada, February 6, 2009.

program and the YBPR are tools which enable Health Canada and the manufacturer to monitor consistency in the vaccine manufacturing process.

Other important elements of the post-licensure regulation of vaccines include Health Canada oversight of post-market changes, as well as inspection and enforcement activities. In the former case, if a sponsor proposes to make changes to a vaccine after being granted marketing authorization (e.g. in terms of clinical indication, dosage, manufacturing or quality specifications), Health Canada must review and authorize all changes that may have an impact on the quality, safety, efficacy or effective use of the product. With regard to inspection and enforcement, the Health Products and Food Branch Inspectorate (HPFBI) – in collaboration with other groups within Health Canada and the PHAC – investigates complaints and problem reports, maintains post-approval surveillance, and manages recalls as required. In addition, regular inspections of vaccine production facilities are conducted as a condition of continued licensing, to ensure that all manufacturing procedures and sites remain GMP-compliant.

## 4.4 Modernization of Regulatory Framework

As many new therapeutic products are expected to be submitted for review by Health Canada within the next few years, it is essential that the regulatory review process undergoes appropriate modernization to reflect evolving science, values and practices across Canada's dynamic health care landscape. Positive modernization of Canada's regulatory system would help to maintain a high standard for patient safety, while expediting approval of innovative products in a timely fashion. In addition, the benefit-risk profile of pharmaceutical and biologic drugs (including vaccines) could be continuously assessed to better manage scientific uncertainty during the approval process.<sup>27</sup> Furthermore, a modernized regulatory system should stimulate innovative research to help ensure the continued health of Canadians, i.e. by providing new mechanisms that will improve understanding of expectations regarding the regulatory submission process, both by Health Canada and regulated drug sponsors.<sup>28</sup> Such modernization should also provide an opportunity to achieve alignment with international policies for regulatory harmonization, thus preventing Canada from inadvertently losing out on its share of global life sciences investment and research – which might otherwise be limited by an uncompetitive regulatory environment. Overall, modernization of Canada's regulatory framework should help to ensure the safety, efficacy and effectiveness of all health products, while supporting timely access to medicines for all Canadians.<sup>29</sup>

### 4.4.1 Bill C-51

Canada's *Food and Drugs Act* – as first adopted in 1953 – is currently in need of updating, not only to address today's challenging environment for drug regulatory review and approval, but also to sustain and constantly improve the efficiency, predictability and transparency of these procedures. With the publishing of its *Blueprint for Regulatory Renewal* in October 2006, and the subsequent tabling of Bill C-51 in April 2008 as the legal groundwork for regulatory modernization within the context of this blueprint, Health Canada has recently taken on the challenge of modernizing Canada's regulatory system for health products for the first time in 40 years.<sup>30</sup>

Bill C-51 was initially introduced by the federal government as an enactment to amend the *Food and Drugs Act*, i.e. to modernize the regulatory system for foods and therapeutic products (i.e. both pharmaceutical and biologic drugs, including vaccines), to strengthen the oversight of the benefits and risks of therapeutic products throughout their life cycle, to support effective compliance and enforcement actions, and to enable a greater transparency and openness of the regulatory system.<sup>31</sup> A companion bill, Bill C-52, was intended to introduce new legislation to regulate the safety of all consumer products, including components, parts or accessories and packaging, that can be reasonably obtained by an individual for non-commercial (including domestic, recreational and sports) purposes.<sup>32</sup> Full details regarding proposed changes to the *Food and Drugs Act* and the *Hazardous Products Act*, including purpose, definitions, prohibitions, authorizations and licenses, powers of the Minister, and offenses are laid out in Bills C-51 and C-52 respectively, as published upon first reading, April 8, 2008.<sup>33,34</sup>

With the call of the October 14, 2008 federal election, the legislation introduced under Bills C-51 and C-52 officially expired. Since the Fall of 2008, the federal government has been expected to re-introduce legislation in the spirit of Bill C-51 aimed at modernizing Canada's regulatory system.<sup>35</sup> As of July 2009, the Bill C-51 has been re-drafted and is awaiting Cabinet approval for introduction to Parliament. The Bill is generally interpreted to have minor amendments, but no major changes, relative to the previous Bill C-51. Additional information and updates are currently being posted at [www.healthycanadians.ca](http://www.healthycanadians.ca). In addition, the current re-draft of Bill C-52 (Bill C-6, also known as the *Canada Consumer Product Safety Act*) was introduced by the federal government on January 29, 2009; this proposed legislation is intended to help keep Canadian families safe from dangerous consumer products. Bill C-6 would replace Part I of the *Hazardous Products Act*, with the purpose of modernizing and strengthening product safety laws by overhauling existing rules to further protect the health and safety of Canadians.<sup>36</sup>

#### 4.4.2 Progressive Licensing Framework

As one major initiative under the recently proposed *Blueprint for Regulatory Renewal*, Health Canada is modernizing the regulatory process for pharmaceutical and biologic products (including vaccines) through a project called the Progressive Licensing Framework (PLF). Since 2006, Health Canada has been developing a new framework consisting of laws, regulations and guidelines that will support timely access to drugs and provide a mechanism for the continuous monitoring and reassessment of a drug's safety, quality and effectiveness throughout its life cycle. The four key elements of this framework include: the adoption of a life cycle approach (Figure 4.1); evidence-based decision-making; good planning; and accountability. Collectively, these elements represent the foundation of the new framework that will support health care professionals and patients in making decisions regarding drug therapy, i.e. by ensuring that they have access to both the drugs and the necessary information to make the best use of them.<sup>37</sup> It is noteworthy that while the PLF term will continue to be recognized, the progressive licensing concept has more recently been referred to under the auspices of "Legislative and Regulatory Modernization".<sup>38</sup> In addition, while proposed changes under the PLF described herein (Section 4.4.2) will guide regulatory oversight of all drugs in Canada (including vaccines), a modernized regulatory framework specific for vaccines is also under development, as described below in Section 4.4.3.

Under Canada's current regulatory system, drug manufacturers are required to file an NDS submission to Health Canada that contains comprehensive information regarding drug safety, efficacy and quality in the context of all scientific, preclinical and clinical studies performed. As described in Section 4.3.2 for vaccine candidates, if the submission is found to comply with the *Food and Drug Regulations*, the manufacturer receives authorization to market the drug in Canada. Within this current "point-in-time" licensing system, relatively few regulatory obligations reside with manufacturers subsequent to market authorization – other than requirements to report adverse drug reactions to Health Canada under strict timelines, submit PSURs as requested, file safety labeling changes based on an analysis of any new "safety signals" that may be observed in the data collected, and provide notification of proposed post-NOC product or process changes (see Section 4.3.3 for specific post-market requirements for vaccines).<sup>39</sup> Under the present system, Health Canada cannot mandate a manufacturer to conduct post-market activities, such as performing studies to assess a drug's long-term safety or potential risks.

Although the current legislation and regulatory system has served Canadians well, Health Canada needs to update its approach to address current realities and emerging challenges. Recent advances in science, medicine and technology underscore the need for a modern regulatory system that can assess new drugs (including complex biologics, such as vaccines and genetic therapies) in a timely manner. In addition, there is a need for enhanced post-market surveillance of drugs, especially in the wake of several recent (voluntary and involuntary) withdrawals of drugs from the market in Canada and abroad.<sup>40</sup> Globally, major regulatory agencies are recalibrating their pre-market evaluation systems to take into consideration the continuously expanding body of knowledge gained throughout a drug's life cycle.

In essence, since drug information increases over time, understanding of drug benefits and risks can change concomitantly. In Canada, the progressive licensing approach would permit assessment of the drug's benefit-risk profile both prior and subsequent to market authorization, and should therefore build greater capacity within the regulatory system to plan for, manage and communicate risks as new information is obtained.<sup>41</sup> As new information emerges, it can be used to optimize drug use for the benefit of patients; this is the ultimate goal of the PLF approach.<sup>42</sup> Health Canada anticipates that progressive licensing will provide several other advantages, for example, the PLF approach should allow increased flexibility to address particular medical needs or exceptional circumstances (such as rare diseases or compassionate use), while permitting better alignment of Canada's regulatory standards with international standards. Additional information regarding the proposed progressive licensing model, including a brief history of Canadian drug regulation, key drivers and rationale behind the development of the PLF, and the main themes upon which it is based, can be accessed on the Health Canada PLF website at [www.hc-sc.gc.ca/dhp-mps/homologation-licensing/index-eng.php](http://www.hc-sc.gc.ca/dhp-mps/homologation-licensing/index-eng.php).

Figure 4.1 – Life-Cycle of Product and Knowledge

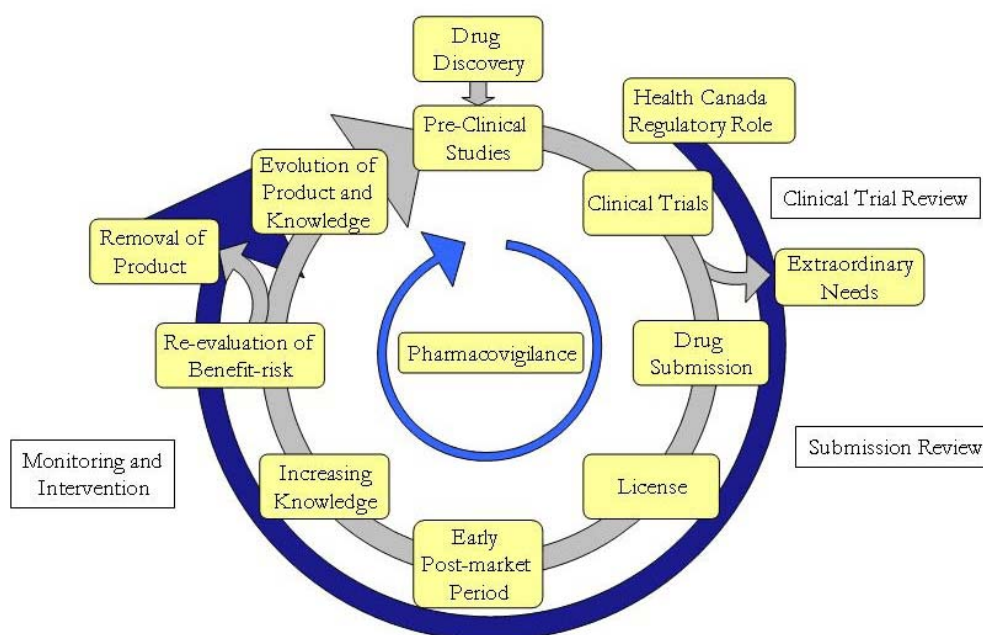


Figure 4.1 illustrates the critical points in the life cycle of a drug and how a regulatory framework can interface with those milestones. A well-designed framework will recognize those critical points and connect the phases between those points to support information collection, analysis, and communication.

Source: The Progressive Licensing Framework Concept Paper for Discussion, Health Canada, 2006; [www.hc-sc.gc.ca/dhp-mps/alt\\_formats/hpfb-dgpsa/pdf/prodpharma/proglic\\_homprog\\_concept-eng.pdf](http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/proglic_homprog_concept-eng.pdf).

Initially, the PLF began with an intensive research phase, with the goal of evaluating the best international regulatory practices used by other regulators to modernize their respective systems. Consultation with stakeholders (including the provinces/territories, health care professionals, industry and patients) took place in 2006 and 2007, and also included an opportunity to provide feedback through the PLF website.<sup>43</sup>

At present, the PLF is still under development, and continues to follow a defined approach to developing a new drug licensing framework.<sup>44</sup> The Progressive Licensing Project team is currently working towards the development of a PLF document, which will incorporate feedback received to date (including legal counsel), and which is expected to provide a “nuts and bolts” representation of how the system will work in real life for drug manufacturers. In unveiling a new regulatory framework, more than new regulations will be required; additional framework components should include guidance documents, processes and practices.<sup>45</sup> It is currently anticipated that the draft framework document will be released subsequent to the introduction of the revised Bill C-51 (see Section 4.4.1), i.e. no earlier than late 2009. Essentially, this framework will provide the outline for implementing the regulations of the revised Bill C-51 that pertain to the PLF. The proposed new regulations will be published (most likely in segments, rather than for the entire framework) in the *Canada Gazette*, Part I, followed by a formal public consultation period. Comments received in response to the republication of the regulations will provide the basis for revisions to the proposed regulations, and the revised regulations will then be published in the *Canada Gazette*, Part II, signaling that the regulations are effective and in force.

To date, significant apprehension has been expressed by vaccine manufacturers (as well as other biologic and pharmaceutical drug sponsors) that the transition to progressive licensing may result in an increasingly onerous regulatory burden, particularly by introducing additional post-market safety standards for vaccines and other drugs on the Canadian market. In addition, it is not clear how other recommendation bodies or procedures – including NACI, the Common Drug Review (CDR) process, and provincial/territorial advisory or formulary committees (see Papers 5 and 6) – may interpret the “life cycle” approach, or whether the introduction of the PLF could delay recommendation/funding decisions while experts wait for additional data throughout a vaccine’s marketed life in the “real world”.<sup>46</sup> Ultimately, there is concern that increasingly stringent regulation (through new post-market testing/reporting requirements) could possibly delay patient access to new vaccines that can prevent future disability and death. As of July 2009, many issues remain unresolved, and the industry awaits further clarification regarding specific procedures and practices (e.g. for individual drugs or product classes) to be introduced under the PLF.

### 4.4.3 Vaccine Regulatory Framework

As another element of recent efforts to modernize Canada's regulatory framework for drug products, Health Canada has undertaken an independent evaluation process to specifically review the current regulatory framework for vaccines for human use in Canada. Historically, the first consolidated version of vaccine regulations in Canada had appeared under the 1955 *Food and Drugs Act*. Specific regulations for polio vaccines were introduced in 1958 and 1963 (live, oral polio vaccine), but no new “product-specific” regulations have been introduced for any vaccine discovered after 1963. Indeed, there have only been minor amendments to the vaccine regulations since the early 1960s.<sup>47</sup> In general, new vaccines are currently regulated under the requirements of Part C, Division 4 of the *Food and Drug Regulations*, applicable to all biologics (Schedule D drugs).<sup>48</sup>

In view of the need to update Canada's regulatory framework for vaccines, a Working Group (consisting of representatives from Health Canada and the PHAC) was created in 2006 to review current vaccine regulations, with the goal of proposing recommendations for enhancing the effectiveness of the vaccine regulatory structure as a transparent, modern, “smart” regulatory framework.<sup>49</sup> The Working Group identified three key sub-projects, encompassing: i) issue identification and gap analysis; ii) requirements for amendments to the regulatory review process (including international filing procedures); and iii) requirements for guidance documents. A formal external consultation process was also initiated in mid-2006 to solicit input directly from vaccine sponsors, as well as from BIOTECanada's Vaccine Industry Committee (VIC),<sup>50</sup> in these key areas. Core issues identified under the three key sub-projects, including highlights of the feedback received through external consultation are presented in Table 4.1. Overall, this first phase of the modernization project (conducted from June to September 2006) revealed several weaknesses, including the current “patchwork” of outdated product-specific and general regulations, and the lack of vaccine-specific guidance documents – particularly in light of modern vaccine technology and manufacturing processes.

Table 4.1 – Vaccines Regulatory Framework

Sub-Project	Issues Identified – Overview of Internal/External Comments
i) Issue identification & gap analysis	<ul style="list-style-type: none"> <li>- Regulations should be forward-looking and flexible to encompass future innovation (e.g. combination vaccines, therapeutic and/or cancer vaccines).</li> <li>- Several sections of regulations are redundant or out-dated (e.g. with respect to expiry dating, storage temperature, reference to units of measurement, and product release testing requirements) and hence should be removed, amended or replaced in guidance documents.</li> <li>- Requirements for specific vaccines should be removed from regulations and addressed in guidance documents.</li> </ul>
ii) Requirements for amendments to the regulatory review process	<ul style="list-style-type: none"> <li>- International harmonization is urgently required, including adoption of systems for e-submissions, based on International Conference on Harmonisation (ICH) standards.</li> <li>- Lot testing should reflect international standards (e.g. final bulk vs final container samples).</li> <li>- Updated review processes are required to assess starting materials, segregation/cross-contamination, and labeling/packaging issues (updated regulations pertaining to these issues would apply to all biologics, not just vaccines).</li> <li>- Enhanced human resources are required at Health Canada, including increased number of highly trained regulatory experts, and opportunities to update skills in vaccine technology.</li> <li>- BGTD should provide clear direction and rationale regarding specific process(es) and data required to support post-NOC changes to biologic products, e.g. via Supplemental NDS or the more efficient notifiable change (NC) process.</li> </ul>
iii) Requirements for guidance documents	<p>Guidance document development/revision will be necessary for:</p> <ul style="list-style-type: none"> <li>- Use of biomarkers (e.g. serum antibody levels as a measure of immune response) as surrogate endpoints for vaccine efficacy (in terms of protection from disease), including biomarker validation. [The use of biomarkers is extremely difficult to standardize, but current reliance on sponsor/published data provides desirable flexibility in the short-term.]</li> <li>- Process validation, including updating of currently available guidelines, e.g. pertaining to sterilization, aseptic processes, and form-fill-seal for pharmaceutical products.</li> <li>- Requirements regarding inspection of finished products (e.g. vials, syringes, ampoules, large volume vs small volume), including particulates and visual inspection methods.</li> <li>- Quality (Chemistry and Manufacturing) section of CTA submissions for Schedule D drugs.</li> </ul>

Sources: i) Hardy, S. Modernization of the Vaccines Regulatory Framework, Update to BIOTECCanada, June 5, 2007; and ii) Blouin, C., Chair, BIOTECCanada Vaccine Industry Committee, Letter to Dr. Nyarko Re: Modernization of the Regulatory Framework for Vaccines for Human Use, September 25, 2006.

With regard to streamlining the current regulatory review process, there was strong consensus regarding the need for regulatory harmonization. Health Canada needs to adopt a global perspective in the assessment of new products, and in this context, the modernization of Canada's vaccine regulatory framework represents an excellent opportunity to achieve alignment with international regulatory standards. By promoting consistency with policies and best practices of other leading regulatory agencies worldwide (particularly in the U.S. and E.U.), harmonization efforts can help to reduce the regulatory burden and associated development costs, while minimizing delays in vaccine approvals – thus facilitating the timely availability of new vaccine technologies to all Canadians.<sup>51,52</sup> Moreover, since Canada represents only approximately 2% of the global vaccine market, a favourable regulatory environment in Canada (based on the principles of global regulatory harmonization) will be critical in terms of ensuring continued access by Canadians to innovative vaccine technologies, as developed both in Canada and abroad.<sup>53</sup>

In June 2007, Health Canada communicated to BIOTECanada's VIC its recommendations for modernizing Canada's vaccine regulatory framework, including the following next steps:<sup>54</sup>

- Revoke all product-specific vaccine regulations in Part C, Division 4, i.e. to provide flexibility to accommodate future vaccine innovation, and to achieve consistency with international vaccine regulatory frameworks
- Prioritize results from (first phase) needs assessment of modernization project, and develop work plan for guidance document development/adoption, ensuring that chosen strategies utilize available international expertise, e.g. to build on World Health Organization (WHO) guidelines
- Update regulations that are applicable to all biologics, establishing a new working group to further develop proposed amendments to Division 4, and working in close coordination with the PLF project.

As of July 2009, industry stakeholders and the public are still awaiting further communication from Health Canada regarding recent progress and the current status of the modernization project for vaccine regulation in Canada. In general, significant work lies ahead in terms of modernizing Canada's overall regulatory system for health products, including biologics such as vaccines. Continued coordination with many individual processes (including the re-drafting/tabling of Bill C-51, and advancement of frameworks for progressive licensing and vaccine regulation in Canada) will be critical within the context of the broader modernization mandate. As part of the modernization process, open consultation and clear, timely communication with vaccine manufacturers and other key stakeholders will be essential in developing improved, efficient regulations to guide relevant vaccine review and approval procedures.

## 4.5 Other Future Considerations in Vaccine Regulation

### 4.5.1 Emerging Therapeutic Vaccines

As described in Paper 3, the recent biotechnology revolution has led to the development of the emerging class of therapeutic vaccines. In contrast to preventive vaccines, therapeutic vaccines are intended to treat an existing disease, rather than provide prophylactic protection. Hence therapeutic vaccines can be administered after infection or disease onset, with the goal of enhancing natural immunity against a specific pathogen, thereby reducing the burden of disease and/or enhancing quality of life.<sup>55</sup> At present, therapeutic vaccine candidates are being evaluated to treat a wide range of disorders, including certain chronic infectious diseases such as acquired immune deficiency syndrome (AIDS) and hepatitis C, as well as non-infectious diseases (e.g. certain cancers, and autoimmune, metabolic, and neurodegenerative disorders).<sup>56,57,58</sup>

Within the context of vaccine regulation, key questions have arisen regarding the future regulatory oversight of emerging therapeutic vaccines worldwide. For example, what regulatory process(es) and bodies will be utilized as novel therapeutic vaccines are brought to market, and will the same safety standards apply as for preventive vaccines? According to research conducted by Canada's Research-Based Pharmaceutical Companies (Rx&D), it can be concluded – from both a scientific and regulatory standpoint – that therapeutic vaccines will not be treated any differently from other biologics within the regulatory systems of several major countries, including the U.S., the United Kingdom and France.<sup>59</sup> Hence it appears likely that therapeutic vaccines will also be regulated as other biologics under Health Canada's BGTD.

However, a major challenge that lies ahead is the need to achieve consensus regarding a definition for the term "therapeutic vaccine"; this may be particularly difficult since vaccines have been traditionally viewed as preventative medicines that prepare the immune system to respond in case of future exposure to a specific pathogen. One recently proposed definition states that therapeutic vaccines are "able to act against a disease by inducing a specific immune response to a micro-organism, a protein or other substance, or a class of cells".<sup>60</sup> Yet the use of this particular definition may open up "grey areas" in which certain vaccines may not precisely fit the definition of traditional preventive or novel therapeutic vaccines. Furthermore, a precise definition of therapeutic vaccines will need to specify whether immunoglobulins and monoclonal antibodies may be included or excluded.<sup>ii</sup> Moreover, certain vaccines may also have both preventive and therapeutic effects, e.g. vaccines targeting the human immunodeficiency virus (HIV), cancer and shingles; these vaccines may fall into a special sub-class. It is thus clear that agreement on definitions and potential sub-classes of therapeutic vaccines is needed, particularly given the rapid pace of technological advancement.

Based on the definition in the preceding paragraph, only three therapeutic vaccines have been approved worldwide, including OncoVAX, Oncophage and CimaVax. Whereas OncoVAX is approved in Switzerland and several eastern European countries for treatment of colon cancer, Oncophage is approved in Russia to treat kidney cancer, and CimaVax is approved in Cuba to treat lung cancer. None of these vaccines have been licensed by Health Canada, the FDA, or the EMEA, and it is not anticipated that these candidates will be approved by these major regulatory agencies in the near-term future.<sup>61</sup> However, as summarized in Paper 3, the arrival of therapeutic vaccines is indeed imminently anticipated in Canada, particularly as both top-tier and emerging Canadian vaccine manufacturers continue to develop a broad range of therapeutic vaccine candidates, e.g. to treat HIV/AIDS, various cancers (including colorectal, prostate, and breast cancers, as well as melanoma) and neurodegenerative diseases such as Alzheimer's and Lou Gehrig's disease.

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<sup>ii</sup> Administration of immunoglobulins (whether monoclonal or not) is normally considered as *passive* immunization, whereas the use of vaccines typically involves *active* immunization – either prophylactic or therapeutic (see Paper 1).

With the anticipated wave of innovative therapeutic vaccines expected to be submitted for approval in the near future in Canada (based on announcements regarding the pipelines of both domestic and foreign drug sponsors),<sup>62,63</sup> it is hoped that Health Canada will provide early opportunities for collaborative, transparent discussions with vaccine manufacturers to clearly define therapeutic vaccines, and to determine the most appropriate mechanisms for their regulation in Canada – ideally, in close alignment with international standards. In addition, it will be important for Health Canada’s BGTD to provide comprehensive scientific expertise across a wider range of (potentially more difficult) disease targets or populations for immunization, some of which had not been thought possible for vaccines in the past.<sup>64</sup> Together, these initiatives should help prevent potential delays in regulatory approvals, thus ensuring the Canadian population has timely, equitable access to new therapeutic vaccines. Papers 5 and 6 also provide further discussion regarding vaccine recommendation procedures and potential funding models for emerging therapeutic vaccines, with the over-arching goal of achieving efficient patient access to these novel vaccine technologies.

## 4.6 Recommendations

Vaccines are currently among the most tightly and best regulated medical products available in the global marketplace.<sup>65</sup> In Canada, vaccines are rigorously reviewed and tested by Health Canada's BGTD to ensure their quality, safety and efficacy before they are licensed for use. Health Canada also monitors the safety and effectiveness of vaccines on an ongoing basis, e.g. through stringent post-market surveillance and lot release programs. With this level of regulatory oversight, vaccines used in Canada are highly effective and safe, and have demonstrated an excellent track record in terms of contributing to the "public good".

At present, Canada's regulatory environment is rapidly evolving, as Health Canada has taken significant steps towards modernizing its regulatory system that governs biologics, pharmaceuticals and other food products, i.e. as part of the proposed *Blueprint for Regulatory Renewal initiative*. For example, Health Canada has proposed several revisions to the *Food and Drugs Act* and the *Food and Drug Regulations* (and/or related guidance documents), particularly as they pertain to the introduction of progressive licensing, an updated vaccine regulatory framework, and subsequent entry biologics (SEBs). As these proposed amendments are further debated and finalized, it is critical that decision-makers recognize the unique, complex characteristics of vaccines and their research challenges – and continue to formulate regulatory policy that ultimately supports timely patient access, and hence efficient immunization program implementation. To this end, and in the spirit of collaboration, the VIC has put forward the following recommendations for consideration by federal/provincial/territorial (F/P/T) governments and other key stakeholders.

### Federal/Provincial/Territorial Recommendations

1. To maximize the medical, social and economic benefits of vaccines for all Canadians, regulatory policies should, at all levels, aim to remove any procedural barriers to the rapid adoption of new immunization programs in Canada, including the development of less duplicative (national) regulatory licensure and (F/P/T) evaluation/recommendation procedures (see Paper 5).
2. In finalizing and implementing its proposed progressive licensing framework (PLF) as a key element of the revised Bill C-51, Health Canada should provide well-defined guidelines that address a life cycle approach that is relevant to the individual drug (or vaccine) and its specific benefit-risk profile – rather than to mandate a single, rigid life cycle approach across all products.
  - Such a flexible, customized approach would minimize the regulatory burden for vaccine manufacturers (particularly in terms of meeting additional post-market testing/reporting requirements under the PLF model), thus minimizing potential delays in patient access to novel vaccine technologies that can prevent future disability and death.
3. With regard to modernizing the regulatory framework for vaccines, Health Canada should develop forward-looking regulations and vaccine-specific guidance documents that reflect the rapid advancement in vaccine technology, clinical research and manufacturing processes, e.g. including: i) the development of combination, therapeutic and/or cancer vaccines; ii) future use of biomarkers as surrogate endpoints for vaccine efficacy; and iii) modern process validation and lot testing methods.
  - Outdated or redundant sections of current regulations (e.g. with respect to storage temperature and expiry date) should be removed, amended or replaced in guidance documents.

4. With respect to emerging therapeutic vaccines, Health Canada should provide early opportunities for collaborative, transparent discussions with vaccine manufacturers regarding appropriate definitions and mechanisms to guide their regulation in Canada, ideally, in close alignment with international standards.
  - In this context, it will be important for the BGTD to provide comprehensive scientific expertise across a wider range of (potentially more difficult) disease targets/populations for immunization.
5. In general, Health Canada's regulatory policies that govern vaccine use should be harmonized with international (ICH) regulatory standards, and aligned where possible with best practices of leading regulatory agencies worldwide (e.g. in the U.S. and E.U.).
  - Harmonization efforts would help to reduce the overall regulatory burden and development costs associated with global vaccine licensure, and will also help to minimize delays in vaccine approval by Health Canada for novel technologies developed both in Canada and abroad.
  - Overall, the development of a modern, flexible, harmonized regulatory system for vaccines will go a long way toward stimulating investment in vaccine research, and helping to secure Canada's position as a leader in the globally competitive field of vaccine development.

#### Stakeholder Recommendations

6. Stakeholders at all levels, including F/P/T government officials, regulatory policy-makers, public health authorities, vaccine manufacturers, academic research institutions, health care professionals, and the general public should actively engage in more frequent interaction and transparent dialogue, thus supporting vaccine manufacturers in meeting the strict (and rapidly evolving) regulatory requirements of Health Canada, while simultaneously satisfying increasing patient demands in terms of understanding vaccine safety, efficacy and effectiveness.
  - In particular, all stakeholders need to take greater responsibility for educating and reassuring the public regarding the increasingly stringent regulatory measures in place to ensure extremely high standards of quality and safety in the research and development, manufacturing, licensing, and use of vaccines in Canada.



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