Evaluation of the Biologics Program
1999-2000 to 2012-2013

Prepared by
Evaluation Directorate
Health Canada and the Public Health Agency of Canada

May 2014
## List of acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADM</td>
<td>Assistant Deputy Minister</td>
</tr>
<tr>
<td>ANDS</td>
<td>Abbreviated New Drug Submission</td>
</tr>
<tr>
<td>AHRA</td>
<td>Assisted Human Reproduction Act</td>
</tr>
<tr>
<td>ATMP</td>
<td>Advanced Therapy Medicinal Products</td>
</tr>
<tr>
<td>BGTD</td>
<td>Biologics and Genetic Therapies Directorate</td>
</tr>
<tr>
<td>BMP</td>
<td>Bilateral Meeting Program</td>
</tr>
<tr>
<td>BP</td>
<td>Biologics Program</td>
</tr>
<tr>
<td>BPI</td>
<td>Bulk process intermediate</td>
</tr>
<tr>
<td>BTOX</td>
<td>Blood, Tissues, Organs and Xenografts</td>
</tr>
<tr>
<td>CAEFISS</td>
<td>Canadian Adverse Events Following Immunization Surveillance System</td>
</tr>
<tr>
<td>CAT</td>
<td>Committee for Advanced Therapies</td>
</tr>
<tr>
<td>CBER</td>
<td>Center for Biologics Evaluation and Research</td>
</tr>
<tr>
<td>CBS</td>
<td>Canadian Blood Services</td>
</tr>
<tr>
<td>CBSA</td>
<td>Canada Border Services Agency</td>
</tr>
<tr>
<td>CBTE</td>
<td>Centre for Blood and Tissue Evaluation</td>
</tr>
<tr>
<td>CERB</td>
<td>Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics</td>
</tr>
<tr>
<td>CFIA</td>
<td>Canadian Food Inspection Agency</td>
</tr>
<tr>
<td>CG II</td>
<td>Canada Gazette II</td>
</tr>
<tr>
<td>CIC</td>
<td>Canadian Immunization Committee</td>
</tr>
<tr>
<td>CIHI</td>
<td>Canadian Institute for Health Information</td>
</tr>
<tr>
<td>CIHR</td>
<td>Canadian Institutes of Health Research</td>
</tr>
<tr>
<td>CPAB</td>
<td>Communications and Public Affairs Branch</td>
</tr>
<tr>
<td>CPSP</td>
<td>Canadian Paediatric Surveillance Program</td>
</tr>
<tr>
<td>CRI</td>
<td>Cost Recovery Initiative</td>
</tr>
<tr>
<td>CSA</td>
<td>Canadian Standards Association</td>
</tr>
<tr>
<td>CTA</td>
<td>Clinical Trial Application</td>
</tr>
<tr>
<td>CTA-A</td>
<td>Clinical Trial Application Amendment</td>
</tr>
<tr>
<td>CTD</td>
<td>Common Technical Document</td>
</tr>
<tr>
<td>CTO</td>
<td>Cells, Tissues and Organs</td>
</tr>
<tr>
<td>CTOSS</td>
<td>Cells, Tissues and Organs Surveillance System</td>
</tr>
<tr>
<td>CVE</td>
<td>Centre for Vaccine Evaluation</td>
</tr>
<tr>
<td>DEL</td>
<td>Drug Establishment Licence</td>
</tr>
<tr>
<td>DHPL</td>
<td>Dear Health Professional Letter</td>
</tr>
<tr>
<td>DIN</td>
<td>Drug Identification Number</td>
</tr>
<tr>
<td>DM</td>
<td>Deputy Minister</td>
</tr>
<tr>
<td>DPD</td>
<td>Drug Product Database</td>
</tr>
<tr>
<td>DPR</td>
<td>Departmental Performance Report</td>
</tr>
<tr>
<td>DSEN</td>
<td>Drug Safety and Effectiveness Network</td>
</tr>
<tr>
<td>EAC</td>
<td>Expert Advisory Committee</td>
</tr>
<tr>
<td>EAP</td>
<td>Expert Advisory Panel</td>
</tr>
<tr>
<td>EBP</td>
<td>Employee Benefit Plan</td>
</tr>
<tr>
<td>EC</td>
<td>European Community</td>
</tr>
<tr>
<td>eCTD</td>
<td>Electronic Common Technical Document</td>
</tr>
<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines and HealthCare</td>
</tr>
<tr>
<td>EMA/EMEA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EPAR</td>
<td>European Public Assessment Report</td>
</tr>
</tbody>
</table>
List of acronyms

EU European Union
EUND Extraordinary Use New Drug
FDALO Food and Drugs Act Liaison Office
FCSAP Food and Consumer Safety Action Plan
FDA Food and Drug Administration (United States)
FTE Full-time Equivalent
GCP Good Clinical Practices
GGP Good Guidance Practices
GMP Good Manufacturing Practices
GoC Government of Canada
GRP Good Review Practices
GVP Good Pharmacovigilance Practices
HDP Human Drugs Program
HESA House of Commons Standing Committee on Health
HIV Human immunodeficiency virus
HPFB Health Products and Food Branch
ICH International Conference on Harmonization on Technical Requirements for Registration of Pharmaceuticals for Human Use
IOM Institute of Medicine
LASA Look-alike Sound-alike
LPL Lipoprotein lipase
LRP Lot Release Program
MAH Market Authorization Holder
MBBNHPB Marketed Biologics, Biotechnology and Natural Health Products Bureau
MHPD Marketed Health Products Directorate
MHPSEIB Marketed Health Products Safety and Effectiveness Information Bureau
MOU Memorandum of Understanding
MPMDB Marketed Pharmaceuticals and Medical Devices Bureau
MRA Mutual Recognition Agreement
NACI National Advisory Committee on Immunization
NAS New Active Substance
NC Non-compliance
NDS New Drug Submission
NIH National Institutes of Health
NOC Notice of Compliance
NOC/c Notice of Compliance with conditions
NOL No Objection Letter
NON Notice of Noncompliance
OAG Office of the Auditor General of Canada
OSCS oversulfated chondroitin sulphate
OMCL Official Medicines Control Laboratories
OSE On site Evaluation
OTC Over-the-counter
PAA Program Activity Architecture
PAAT Post-authorization activity table
PBRER Periodic Benefit Risk Evaluation Report
### List of acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDP</td>
<td>Pharmaceutical Drugs Program</td>
</tr>
<tr>
<td>PEAC</td>
<td>Paediatric Expert Advisory Committee</td>
</tr>
<tr>
<td>PER</td>
<td>Positron-emitting Radiopharmaceutical</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>PHAC</td>
<td>Public Health Agency of Canada</td>
</tr>
<tr>
<td>PIC/S</td>
<td>Pharmaceutical Inspection Cooperation Scheme</td>
</tr>
<tr>
<td>PLR</td>
<td>Physician Labelling Rule</td>
</tr>
<tr>
<td>PMRC</td>
<td>Post Market Reporting Compliance</td>
</tr>
<tr>
<td>PMS</td>
<td>Performance Measurement Strategy</td>
</tr>
<tr>
<td>PPIAD</td>
<td>Policy, Planning and International Affairs Directorate</td>
</tr>
<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
</tr>
<tr>
<td>PSUR-C</td>
<td>Periodic Safety Update Report-Confirmatory</td>
</tr>
<tr>
<td>PVP</td>
<td>Pharmacovigilance Plan</td>
</tr>
<tr>
<td>Q&amp;A</td>
<td>Question and Answer</td>
</tr>
<tr>
<td>QMS</td>
<td>Quality Management System</td>
</tr>
<tr>
<td>RAPB</td>
<td>Regions and Programs Bureau</td>
</tr>
<tr>
<td>RCC</td>
<td>Regulatory Cooperation Council</td>
</tr>
<tr>
<td>REB</td>
<td>Research Ethics Board</td>
</tr>
<tr>
<td>REMS</td>
<td>Risk Evaluation and Mitigation Strategy</td>
</tr>
<tr>
<td>RMOD</td>
<td>Resource Management and Operations Directorate</td>
</tr>
<tr>
<td>RMP</td>
<td>Risk Management Plan</td>
</tr>
<tr>
<td>SANDS</td>
<td>Supplemental Abbreviated New Drug Submission</td>
</tr>
<tr>
<td>SAP</td>
<td>Special Access Program</td>
</tr>
<tr>
<td>SBD</td>
<td>Summary Basis of Decision</td>
</tr>
<tr>
<td>SEB</td>
<td>Subsequent Entry Biologic</td>
</tr>
<tr>
<td>SIMS</td>
<td>Stakeholder Information Management System</td>
</tr>
<tr>
<td>SNDS</td>
<td>Supplemental New Drug Submission</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>SSCSAST</td>
<td>Senate Standing Committee on Social Affairs, Science and Technology</td>
</tr>
<tr>
<td>TAS</td>
<td>Therapeutic Access Strategy</td>
</tr>
<tr>
<td>TBS</td>
<td>Treasury Board of Canada Secretariat</td>
</tr>
<tr>
<td>TESS</td>
<td>Transfusion Errors Surveillance System</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
</tr>
<tr>
<td>TPD</td>
<td>Therapeutic Products Directorate</td>
</tr>
<tr>
<td>TPSI</td>
<td>Therapeutic Product Safety Initiative</td>
</tr>
<tr>
<td>TTISS</td>
<td>Transfusion Transmitted Injuries Surveillance System</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>vCJD</td>
<td>Variant Creutzfeldt-Jakob disease</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>YBPR</td>
<td>Yearly Biologic Product Report</td>
</tr>
</tbody>
</table>
# Table of Contents

Executive Summary ........................................................................................................................ ii

Management Response and Action Plan .......................................................................................... xv

1.0 Introduction ................................................................................................................................. 1

   1.1 Organization of the report ........................................................................................................ 1

2.0 Profile of the Biologics Program .............................................................................................. 1

   2.1 Roles and responsibilities of program partners ...................................................................... 2
   2.2 Program activities and logic .................................................................................................. 7
   2.3 Resources ............................................................................................................................ 10
   2.4 Program context .................................................................................................................... 10

3.0 Evaluation methodology ........................................................................................................... 11

   3.1 Evaluation design and methods ............................................................................................ 11
   3.2 Reporting .............................................................................................................................. 14
   3.3 Limitations of the methodology and mitigation strategies ................................................... 14

4.0 Findings – relevance .................................................................................................................. 15

   4.1 Ongoing need ......................................................................................................................... 15
   4.2 Alignment with federal priorities ........................................................................................ 21
   4.3 Consistency with federal roles and responsibilities ............................................................. 24

5.0 Findings: governance and implementation .............................................................................. 25

   5.1 Program governance ............................................................................................................. 25
   5.2 Collaboration with external partners .................................................................................... 26
   5.3 Performance measurement .................................................................................................. 27
   5.4 Program implementation ....................................................................................................... 27

6.0 Findings – outcomes achieved ................................................................................................. 76

   6.1 Stakeholder awareness and understanding ............................................................................ 76
   6.2 Industry awareness and understanding ................................................................................ 78
   6.3 Safety and effectiveness ....................................................................................................... 79
   6.4 Industry compliance ............................................................................................................. 81
   6.5 Adoption of safe behaviours ............................................................................................... 83
   6.6 Use of scientific evidence and risk-benefit analysis ........................................................... 84
   6.7 Timely regulatory response to risks .................................................................................... 86
   6.8 International harmonization ............................................................................................... 90
   6.9 Long-term outcomes ............................................................................................................ 92
   6.10 Unintended consequences ................................................................................................. 93

7.0 Findings – efficiency and economy .......................................................................................... 94

8.0 Conclusions and recommendations ........................................................................................ 99

Appendix A – Evaluation Matrix ..................................................................................................... 111

Appendix B – List of References .................................................................................................... 121

Appendix C – Supplementary Data Tables ................................................................................... 131
Executive Summary

The Biologics Program (BP) is managed through the Health Products and Food Branch (HPFB) of Health Canada. The BP regulates drugs and products derived from living sources, as well as radiopharmaceuticals. Products derived from living sources include blood and blood components and blood products; vaccines; hormones; enzymes; cytokines; monoclonal antibodies; gene therapy products; cells, tissues, and organs; xenografts; and semen for assisted conception.

The main program partners involved in delivering the BP are the Biologics and Genetic Therapies Directorate (BGTD), the Therapeutic Products Directorate (TPD), the Marketed Health Products Directorate (MHPD), the HPFB Inspectorate (the Inspectorate), the Regions and Programs Bureau (RAPB), the Policy, Planning and International Affairs Directorate (PPIAD) and the Resource Management and Operations Directorate (RMOD). Program activities include creating and maintaining the regulatory framework, interacting and communicating with partners and stakeholders, performing risk-benefit assessments, conducting post-market monitoring and surveillance, and compliance and enforcement.

The evaluation of the BP is part of Health Canada’s Five-Year Evaluation Plan. In accordance with the Treasury Board Policy on Evaluation (TBS, 2009), the evaluation assessed the relevance and performance (effectiveness, efficiency, and economy) of Health Canada’s activities under the program. The evaluation covered the period from 1999 to the end of calendar year 2012, with an emphasis on the last five years, although the report also reflects program activities up to the end of December 2013. The results of the evaluation will inform the implementation of current and future program activities.

An independent evaluation consulting firm conducted the evaluation on behalf of Health Canada. The evaluation drew on several lines of evidence, including literature review, document review, review of administrative data, case studies, surveys of manufacturers and other stakeholders, key informant interviews with external and internal stakeholders, and a focus group with cell, tissue, and organ (CTO) establishments. This report presents the evaluation findings, draws conclusions, and makes recommendations.

Findings

Relevance

There is an ongoing need for continued oversight by Health Canada to help protect the health and safety of Canadians. Increased use of biologics is exposing more Canadians to the risks, as well as the benefits of these products. Health Canada’s role is consistent with federal and Health Canada roles and responsibilities.

The evaluation confirmed an ongoing need for government oversight of biologics in order to help protect the health and safety of Canadians. Biologics contribute significantly to the health of Canadians and represent an important component of the Canadian health care system. Moreover, while biologics are frequently used in the treatment of rare diseases, their use in treating more
common, long-term conditions (such as diabetes, cardiovascular disease, digestive disorders and asthma) is growing. Currently, four of the five top-selling drugs in Canada, and five of the top ten, are biologics. As use of these products grows due to demographic factors, as well as marketing by industry, more Canadians will be exposed to the risks, as well as the benefits, of these products. Moreover, trends such as the emergence of innovative therapies and products, combination products, and globalization of the supply chain are creating uncertainties that further support the need for government intervention to help protect the health and safety of Canadians. Such a role, furthermore, is consistent with federal and Health Canada roles and responsibilities, as described in federal statutes and regulations, and aligns directly with Health Canada’s strategic outcome to inform Canadians and protect them from health risks associated with food, products, substances, and environments.

The BP is aligned with federal priorities to improve the safety of health products through regulatory modernization.

BP activities are well-aligned with federal priorities to strengthen consumer safety. The federal government has devoted substantial resources over the past decade to broader initiatives intended to improve the safety of health products, including biologics, through modernizing the regulatory framework for these products. Key principles of regulatory modernization include adopting a product lifecycle approach, whereby the risks and benefits of therapeutic products are assessed over their entire lifecycle; adopting regulatory interventions proportional to risk; and enhancing the transparency and openness of the regulatory system.

Performance — program implementation

Over the period of the evaluation, Health Canada has made progress in implementing its planned activities and, in the process, has responded to several emergent issues and challenges. However, a number of unresolved issues and challenges remain.

Legislative and regulatory development

**Health Canada has developed comprehensive regulatory frameworks to address the risks associated with cells, tissues and organs and blood and blood components, and work is ongoing to develop regulations for orphan drugs and to modernize the existing vaccine**

Over the period of the evaluation, Health Canada developed comprehensive regulatory frameworks to address the risks associated with cells, tissues and organs (CTO) and blood and blood components. National CTO standards were implemented in 2003, and Phase I of the Safety of Human Cells, Tissues and Organs for Transplantation Regulations (the CTO Regulations) came into force in December 2007. The Regulations included provisions related to CTO establishment registration; quarantine; errors, accidents, and adverse reactions; reporting to Health Canada; and quality assurance systems, among others. Health Canada is continuing to develop Phase II of the CTO regulatory framework, which will include more comprehensive compliance monitoring and enforcement provisions, as well as surveillance and adverse reaction reporting strategies. Phase II will also extend to heart valves and dura mater; these products will transition from the Medical Devices Regulations to the CTO Regulations.
Health Canada is currently in the process of finalizing a new regulatory framework for blood and blood components, which will constitute its final response to the 1997 recommendations of the Commission of Inquiry on the Blood System in Canada (the Krever Commission). As with the CTO Regulations, Health Canada took a staged approach to developing the blood regulatory framework, which included implementing a new establishment licensing process for blood establishments; updating the plasmapheresis regulations; and implementing blood standards. The *Blood Regulations* were published in Canada Gazette II in October 2013 and are expected to come into force in October 2014.

Health Canada is currently developing a regulatory framework for the development, evaluation, and approval of orphan drugs, which are drugs (often biologics) developed specifically for the treatment of rare diseases. In addition, updates to the regulatory framework for vaccines for human use and for donor semen are planned for future phases of regulatory modernization. With respect to donor semen, BGTD is considering options to keep pace with new techniques for extraction, freezing, and storage that have been developed in the past few years. Although there have been a number of challenges to putting regulations in place under the *Assisted Human Reproduction Act (AHRA)*, including a constitutional challenge by the Province of Quebec, policy discussions and analysis of options are currently underway.

Other emerging biologic therapies, such as stem cell therapy and gene therapy, are currently treated as drugs under existing regulation. This is similar to the United States’ (US) approach, but different from the European Union (EU), where a dedicated regulatory framework for advanced therapy medicinal products has been in place since 2007. Both the US and the EU, unlike Health Canada, have established multi-disciplinary advisory committees that review and evaluate data relating to the safety, effectiveness, and appropriate use of advanced treatments, although it is important to note that the committee approach is used for all products, not just advanced therapies.

Health Canada currently treats submissions for subsequent entry biologics (SEBs) as New Drug Submissions (NDS) under the existing regulatory framework. The biologics industry perceives a need for clearer guidance with respect to emerging biologic therapies and favours including SEBs in Health Canada’s regulatory modernization initiatives. BGTD representatives noted that experience will inform whether regulatory amendments are necessary.

Clinical trials

**Health Canada has taken numerous steps to strengthen the regulatory framework for clinical trials, but does not currently require sponsors to disclose the results of clinical trials.**

Health Canada has strengthened the regulatory framework for clinical trials by implementing risk-based approaches to monitoring clinical trial adverse reaction reports, introducing an inspection program for clinical trial sites, and commissioning the development of new voluntary standards for Research Ethics Boards. In response to concerns that the requirement to file a Clinical Trial Application (CTA) was posing an undue burden on researchers using positron-emitting radiopharmaceuticals (PERs), Health Canada implemented regulations defining which types of basic clinical research studies involving PERs fall outside the clinical trial regulations, and which require a CTA.
Most recently, in May 2013, Health Canada launched a new public database of drug clinical trials it had authorized. Though mandatory for sponsors, the database contains more limited information than the registries that have been mandatory in the US since 1997 and the EU since 2004. Furthermore, unlike the US (and soon the EU), Health Canada does not require sponsors to disclose the results of clinical trials. Further enhancing the amount of clinical trial information it makes publicly available, including the results of clinical trials, would be consistent with Health Canada’s commitment to enhancing transparency and openness as part of regulatory modernization, and would further align its approach with its main international counterparts.

**Recommendation 1:**

Consistent with international trends and its commitment to enhancing transparency and openness under regulatory modernization, Health Canada should further enhance the amount of clinical trial information it makes publicly available, including the results of clinical trials.

Submission review and market authorization

BGTD has met its performance targets for first review of biologics submissions since 2006. It is unknown how frequently OSEs and LRP evaluations identify issues that could affect the quality or safety of a product, and it is unclear if the BP collects this information in a systematic way.

Health Canada achieved a major milestone with the coming into force of the *Fees in Respect of Drugs and Medical Devices Regulations* in April 2011. The Regulations updated user fees for various regulatory services, including submission review and drug establishment licensing, with the goal of restoring the cost-sharing ratio of 50% that existed when user fees were first introduced in 1995. The increase in revenues stemming from updated user fees is expected to contribute to a stable funding platform that will improve Health Canada’s ability to provide regulatory services.

That said, it is important to note that BGTD has met its performance targets for first review since 2006, well before updated user fees were implemented. Furthermore, while the timeliness of submission review has fluctuated over the period of the evaluation, in both 2011 and 2012, 100% of biologics NDS and Supplemental New Drug Submissions (SNDS) review cycles were completed within the service standard.

BP representatives expressed concern that the updated user fees did not take into account the higher costs of biologics submissions compared to pharmaceutical submissions. These higher costs stem from the greater complexity of biologics submissions and from the extra costs associated with On-site Evaluations (OSEs) and the Lot Release Program (LRP). OSEs are routinely conducted for new product types and changes to biologics manufacturing processes and facilities as part of the review process; their purpose is to confirm the information in the submission and make sure that there are no previously unforeseen factors that could result in a poor-quality product or increase the likelihood in the future of an error or accident that could lead to a contaminated product. Between 2000 and 2005, eight Notices of Deficiency were issued based on the outcome of OSEs.
The LRP is a risk-based program covering both pre- and post-market stages. Given that biologics involve the use of living organisms that are inherently more variable, difficult to consistently produce and characterize, and more sensitive to changes in starting materials and manufacturing than chemically synthesized drugs, the LRP is intended to provide additional monitoring of these products to help ensure their safety and efficacy. Products subject to the LRP are assigned to one of four Evaluation Groups, each of which corresponds to a different level of regulatory oversight based on product risk levels.

The evaluation could not determine how frequently OSEs and LRP evaluations identify issues that could affect the quality or safety of a product, and it is unclear if the BP collects this information in a systematic way.

**Recommendation 2:**

Health Canada should maintain data on the frequency with which OSEs and LRP evaluations identify issues with potential implications for product quality and safety. This information could help to demonstrate the importance of, and need for, these unique components of the BP.

Like OSEs and the LRP, regulatory research is another unique element of the BP that does not exist within the Pharmaceuticals Program. The research performed is a combination of 1) forward-looking research to anticipate new issues in the regulation of biologics, and 2) tactical method development and problem-solving. The former often informs policy development in emerging areas of regulation, whereas the latter supports the pre-market review, as well as the post-market functions of the BP through, for example, developing new methods to support the evaluation of biologics, or conducting laboratory analyses to support Inspectorate activities. Work is ongoing to develop a governance framework that will allow the research function to be a readily-available resource to all partner directorates in the BP, while still performing the type of forward-looking research that can inform policy development. Over the past several years, the research function has reportedly been encountering some significant resource challenges.

Post-market surveillance

**Health Canada has taken numerous steps to improve post-market surveillance of biologics, while there are ongoing challenges with adverse reaction reporting for biologics and the use of adverse reaction report data. Health Canada lacks a standardized approach and centralized mechanism for systematically tracking its signal activities and its response to the recommended actions arising from completed signal assessments.**

Over the period of the evaluation, Health Canada has taken a number of steps to improve post-market surveillance, including implementing electronic adverse reaction reporting for health care professionals and, more recently, for industry. Most recently, on December 6, 2013, Bill C-17, the *Protecting Canadians from Unsafe Drugs Act* (Vanessa’s Law) was announced and is currently in second reading. This legislation proposes changes to the *Food and Drugs Act* that are expected to improve Health Canada’s ability to collect post-market safety information, including a proposed amendment introducing mandatory reporting of adverse reactions by health care institutions. The CTO Regulations and the proposed new *Blood Regulations* both already
include provisions for mandatory reporting by health care institutions for certain types of adverse reactions.

Despite progress in these areas, there remain some challenges associated with adverse reaction reporting for biologics and the use of adverse reaction report data by Health Canada. Some of these challenges stem from the fact that, in addition to Health Canada, the Public Health Agency of Canada (PHAC) and the provinces and territories also have responsibilities for post-market surveillance of blood, CTO, and vaccines. This introduces the potential for confusion among stakeholders regarding adverse reaction reporting obligations, as well as the possibility of under-reporting to the Canada Vigilance Program, Health Canada’s adverse reaction reporting system. Although Health Canada and PHAC regularly collaborate to reconcile adverse reaction report data for these products in their respective databases, confidentiality provisions prevent Health Canada from directly accessing PHAC and provincial/territorial databases. As a result, Health Canada does not have access to comprehensive adverse reaction report data for these products, which limits the usefulness of these data for the purpose of post-market surveillance. Notably, the 2010 Lessons Learned Review on the PHAC/Health Canada response to the 2009 H1N1 pandemic recommended that the parties involved (PHAC, Health Canada, and the provinces and territories) finalize agreements on sharing vaccine surveillance information across jurisdictions and implement an integrated surveillance system for immunization, including monitoring adverse events.

Although Health Canada has begun developing and implementing strategies such as targeted surveillance and data mining to systematically monitor adverse reaction reports in the Canada Vigilance Program for potential safety signals, the latter is likely to have limited usefulness for post-market surveillance of biologics in the near term. This is because many biologic products are used in small populations and therefore are unlikely to generate a sufficient number of adverse reaction reports in the Canada Vigilance Database to support data mining. While Health Canada does carry out targeted surveillance using Canada Vigilance data for targeted adverse events in relation to specific, targeted drugs, it relies more extensively on other sources for post-market safety information, including international data, information provided by market authorization holders (e.g., Periodic Safety Update Reports, or PSURs), and individual case study reports. That said, as the use of biologics to treat more common conditions becomes more widespread, data-mining may become more important in future as a means of identifying potential safety signals.

Currently, Health Canada lacks a standardized approach and centralized mechanism for systematically tracking its signal activities and its response to the recommended actions arising from completed signal assessments. At present, this information is inconsistently maintained and highly dispersed across HPFB. A tracking tool for safety recommendations for pharmaceuticals has recently been introduced, and according to BP representatives, a system to monitor outcomes of biologics signals will be considered for future implementation. Given the potential implications for the health and safety of Canadians, a comprehensive, consistent, and centralized approach to information management for Health Canada’s post-market surveillance activities seems warranted.
**Recommendation 3:**

Health Canada should improve its information systems for post-market surveillance and monitoring. In particular, Health Canada should develop and implement a comprehensive and centralized approach to information management for post-market surveillance activities. This should include a centralized mechanism for tracking signal activities related to biologics, including Health Canada’s response to the recommended actions arising from completed biologics signal assessments.

Despite announcing plans to do so under the Food and Consumer Safety Action Plan (FCSAP), Health Canada has not implemented some elements of a strengthened approach to post-market surveillance that are in place elsewhere, namely the authority to compel manufacturers to submit risk management plans (RMPs) and PSURs. However, the recently announced Bill C-17 proposes an amendment to the *Food and Drugs Act* that would allow Health Canada to require persons to provide information within their control for the purpose of assessing serious risks to health, and to require manufacturers to compile information, conduct new tests or studies, and/or monitor experience, for the purpose of obtaining additional information. Bill C-17 also proposes to authorize Health Canada to impose terms and conditions on market authorizations and to amend these terms and conditions when necessary.

While the latter authority is considerably broad, it is unclear if Health Canada has specific plans to compel RMPs in future. Another area of uncertainty is the extent to which Health Canada monitors manufacturers’ compliance with the conditions imposed as part of Notices of Compliance with Conditions (NOC/cs).

**Recommendation 4:**

Health Canada should examine whether there is an ongoing rationale for pursuing the authority to compel manufacturers to submit risk management plans as per its commitment under the FCSAP.

**Compliance and enforcement**

Health Canada has taken a number of steps to strengthen compliance and enforcement. Challenges remain related to GMP reporting by product line.

In the area of compliance and enforcement, Health Canada has strengthened clinical trial inspections by developing risk criteria for site selection; strengthened oversight over imported products through the National Border Integrity Program; introduced a Good Pharmacovigilance Practices (GVP) inspection program; and adopted a risk-based approach to Good Manufacturing Practices (GMP) inspections of domestic drug establishments.

Health Canada and the US Food and Drug Administration (FDA) have recently launched an initiative under the Regulatory Cooperation Council (RCC) that aims to increase each country’s reliance on GMP inspection reports prepared by the other country. Currently, the initiative applies to sites in Canada and the US, although it may be expanded to other jurisdictions in the future. Although a key focus of the RCC initiative is the standardizing and sharing of GMP inspection reports, Health Canada and the FDA differ in their reporting approaches. While the
FDA reports by product category, Health Canada aggregates GMP reporting for pharmaceutical, biologic and veterinary drugs. Achieving the objectives of the initiative may require a common approach to compliance reporting.

Bill C-17, which was announced on December 6, 2013, proposed amendments that would give Health Canada the power to recall therapeutic products from the market when they present an imminent or serious risk to health. The amendments also include increased fines and penalties up to a maximum of $5,000,000 and/or two years in prison. These amendments, if implemented, would address the concerns expressed by some key informants about what they perceive as the relatively limited enforcement options that are currently available to Health Canada.

Communications and stakeholder engagement

**Health Canada has undertaken a number of initiatives to improve communications and stakeholder engagement.**

Health Canada has undertaken a number of initiatives to improve communications and stakeholder engagement. For example, since 2005, Health Canada has provided the public with information about review decisions through Summary Basis of Decision (SBD) documents. In 2012, in part to address concerns expressed by the Office of the Auditor General (OAG) that it was not disclosing information related to NOC/cs, rejections, and withdrawals of new drugs, Health Canada introduced the post-authorization activity table (PAAT). PAATs provide ongoing information about approved products. They include a brief summary of activities that affect the safe and effective use of the product, such as information related to submissions for a new use of the product (whether Health Canada’s decision was positive or negative), submissions filed in order to meet conditions (for products approved under the NOC/c Guidance), and regulatory decisions such as the cancellation of the Drug Identification Number (DIN). Health Canada does not publish SBDs for negative decisions or otherwise provide information to the public about the reasons for negative decisions, unlike the FDA and the European Medicines Agency (EMA). However, beginning in 2014–2015, Health Canada will begin publishing summaries of post-market drug safety reviews.

To improve the quality and availability of easy-to-understand drug product labelling, Health Canada has enhanced the product monograph and introduced regulatory amendments under the Plain Language Labelling Initiative. At present, Health Canada has limited authority to require manufacturers to modify product labelling once a product has received a Notice of Compliance. This shortcoming is addressed by Bill C-17, which would give Health Canada the authority to require manufacturers to modify a product label or to modify or replace its package in order to prevent injury to health.

Over the period of the evaluation, Health Canada has disseminated risk and safety information through the “advisories, warnings and recalls” page on the MedEffect website and a variety of other dissemination mechanisms. In early 2013, Health Canada launched the Recalls and Safety Alerts Database, which includes an advanced search feature and a new format for risk communications. Health Canada indicated that it is currently in the process of reviewing its existing performance targets for the content development of risk communications and the dissemination of risk communications, and is looking at areas where more focused
improvements in risk communications could be made. Health Canada also recently initiated an evaluation of its risk communications for health products, including biologics, following through on long-standing plans to assess the effectiveness of its risk communications products.

Health Canada provides a variety of opportunities for stakeholder engagement, such as holding public consultations on proposed guidance, policies, and regulatory amendments and establishing advisory committees to guide regulatory and policy development. In addition, Health Canada consults with industry through pre-submission meetings and the Bilateral Meeting Program (BMP). While these specific opportunities are not available to health care practitioners and consumers/patients, Health Canada indicated that it does meet with industry associations, hospital associations, and medical associations representing health care practitioners. Some external key informants expressed concern that the engagement and consultation process may favour industry over other stakeholders.

**Performance — outcomes achieved**

Over the period under evaluation, Health Canada has engaged in many activities that are expected to contribute to the outcomes of the BP. However, for various reasons, data to support definitive conclusions on outcomes achieved are relatively limited.

Immediate outcomes

**There are opportunities to improve awareness and understanding of drug safety information among consumers and health professionals.**

In the immediate or short term, Health Canada’s activities are expected to produce increased awareness and understanding by non-industry stakeholders of risks and benefits related to biologics. Surveys conducted between 2003 and 2007 identified opportunities to improve awareness among both consumers and health professionals of drug safety information available from Health Canada, although information specific to biologics was not available. Health Canada is currently in the process of evaluating the effectiveness of its risk communications.

**There are opportunities to improve awareness and understanding of pre-market activities among industry.**

In the immediate term, Health Canada’s activities are expected to produce increased awareness and understanding among industry of Health Canada’s regulatory activities for biologics. The available evidence, though limited, points to some potential areas for improvement. Areas where greater clarity may be required include the classification of stem cell, gene therapy, and other emerging health products; naming of SEBs; classification of CTO products; classification of some combination products; and Health Canada’s use of foreign reviews and guidance in the review process.
There are pre-market and post-market processes in place that are intended to help ensure that biologics are safe and effective.

In the short term, Health Canada’s activities are also intended to produce increased safety and effectiveness of biologics. There are pre-market and post-market processes in place that are designed to help ensure that biologics are safe and effective, but no concrete evidence of improvements in these areas.

The available data suggests that serious industry non-compliance is relatively uncommon. There are opportunities to improve compliance reporting by focusing to a greater extent on outcomes and disaggregating compliance reporting by product line.

Finally, in the short term, Health Canada’s activities are expected to lead to increased industry compliance with regulatory requirements. The available data suggest that serious non-compliance is relatively uncommon. Over the period of the evaluation, however, Health Canada has not reported regularly or consistently on the nature, seriousness, frequency, or prevalence of non-compliances related to biologics, and has focused its reporting, instead, on quantifying activities and outputs. Furthermore, much of Health Canada’s compliance data, including GMP, Good Clinical Practice (GCP), and GVP compliance data, is aggregated across multiple product categories, encompassing human drugs and biologics.

That said, the Inspectorate has recently developed an annual inspection summary report that will be published on the Health Canada website. The 2012–2013 report includes a description of Inspectorate activities and outputs, describes the overall compliance rate of industry, and lists the common observations cited in non-compliant establishments. The report does not contain any information on actions taken by the Inspectorate in response to non-compliance, nor does it break down GMP, GCP and GVP compliance information by product category. However, inspection and compliance information for semen, blood and CTO are reported by product category.

There are number of challenges to disaggregating compliance reporting, including technical difficulties in extracting the necessary data. In addition, while the pre-market function of the BP is aligned around the product, this is not necessarily true of the compliance function, which is oriented around processes. Thus, a GMP inspection of a manufacturing facility that produces both pharmaceuticals and biologics focuses on the overall manufacturing process, not on the products manufactured there, and the inspection outcome is applicable to the facility as a whole. That said, similar constraints do not present themselves with respect to GCP inspections. Clinical trials involve a single product, which is either a pharmaceutical or a biologic, and therefore clinical trial inspection data could more easily be reported by product type. In the context of Health Canada’s current Program Activity Architecture, in which the Pharmaceuticals Program and the Biologics Program are distinct program areas, there is a need to report program-specific inspection and compliance data.
**Recommendation 5:**

Health Canada should build on its current approach to compliance reporting by increasing its emphasis on compliance and enforcement outcomes, and enhancing its ability to report biologics-specific GMP, GVP, and GCP inspection and compliance data.

Intermediate outcomes

The extent to which Health Canada activities have led stakeholders to adopt safe behaviours is unknown. Health Canada’s ongoing evaluation of the effectiveness of its risk communications may shed light on this question.

In the intermediate term, Health Canada activities are expected to lead stakeholders, in particular health care professionals and consumers, to adopt safe behaviours with respect to the use of biologics. Nonetheless, the extent to which Health Canada’s activities may influence these behaviours is unknown. Health Canada’s ongoing evaluation of the effectiveness of its risk communications may provide insights into the degree to which its activities have influenced stakeholder behaviour.

The use of scientific evidence and risk-benefit analysis (and/or risk-based analysis) is formally incorporated into Health Canada’s pre-market and post-market processes.

Health Canada activities are also expected to result in increased use of scientific evidence and risk-benefit analysis to inform decision making related to biologics. The use of scientific evidence and risk-benefit analysis is formally integrated into Health Canada’s Decision-Making Framework for Identifying, Assessing and Managing Health Risks, and also into various pre-market and post-market processes. Health Canada has established a number of Expert Advisory Committees to provide guidance on regulatory and policy development, and has implemented some of their recommendations. For example, development of the CTO and Blood Regulations were both informed by input from committees of external experts.

Recognizing that policy and regulatory development is often a lengthy process, there are instances in which Health Canada’s response has taken longer than expected to implement. The overall timeliness of the biologics signal process (i.e., from signal detection to ultimate action taken by Health Canada) could not be determined.

In the intermediate term, Health Canada hopes to achieve a timely response to identified risks related to biologics. Recognizing that policy and regulatory development is often a lengthy process, the evaluation found some instances in which Health Canada’s response has taken longer than expected to implement. Both the CTO and the Blood Regulations, for example, took more time and resources to complete than originally planned.

Analysis of Health Canada’s signal data revealed that biologics signals are assigned for assessment in a timely fashion and that a large majority of biologics signal assessments are completed within the service standard of 130 days. Due to a limited number of cases, the evaluation was unable to draw conclusions about the overall timeliness of the biologics signal process (i.e., the total time elapsed from signal detection to ultimate action taken by Health Canada).
Health Canada is actively engaged in a variety of international fora. Health Canada is viewed by international key informants as a constructive participant in bilateral and multilateral engagement.

In the intermediate term, Health Canada expects to achieve increased international harmonization of regulatory requirements for biologics. Among many other international engagements, Health Canada is an official observer to and participant in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH); has developed Mutual Recognition Agreements (MRAs) on GMP compliance with a number of other jurisdictions; has formal information-sharing agreements with the FDA, Australia’s Therapeutic Goods Administration (TGA), and the European Community; and participates with the FDA in the RCC, the overall goal of which is to better align the two countries’ regulatory approaches.

BGTD serves as a prequalification authority for the World Health Organization’s (WHO) Vaccine Prequalification Network, and is a founding member of the WHO’s Blood Regulators Network. BGTD also helped to develop the WHO’s GMP for Blood Establishments, contributed to the WHO’s guidance document on follow-on biosimilars, and was recently confirmed as a WHO Laboratory Collaborating Centre for Biologics to verify international standards for influenza vaccines. International key informants view Health Canada as a constructive participant in bilateral and multilateral engagement.

Long-term outcomes

**Health Canada’s activities have likely contributed to a reduced exposure to health risks and fewer adverse reactions.**

In the long term, Health Canada’s activities will likely contribute to reduced health risks and adverse events associated with the use of biologics. The available survey data show a high level of confidence among consumers in the safety of drugs and the regulatory system, though information specific to biologics is not available.

Ultimately, Health Canada hopes to achieve a sustainable, cost-efficient, responsive, and science-based regulatory system for biologics in Canada. The evaluation found that Health Canada uses scientific evidence and consults with stakeholders in policy and regulatory development. While recent updates to user fees for biologics help to support the sustainability of the regulatory system for biologic drugs, BP representatives noted that the fees did not consider the greater complexity of biologics submissions or the extra costs associated with OSEs and the LRP. Furthermore, other product lines such as CTO and blood products are not cost-recovered.

**Performance — efficiency and economy**

Program performance and financial information was insufficient to properly demonstrate efficiency and economy. HPFB has recently implemented a number of improvements to its approach to financial reporting, which should facilitate future analysis.

Changes in HPFB’s approach to financial reporting over the period of the evaluation made it challenging to consistently match BP expenditures and budgets, so as to compare and analyze this
HPFB has recently restructured its financial reporting to comply with federal government requirements, which should improve the accuracy of this information and facilitate future analysis.

Activity-based financial reporting has not taken place since 2008–2009. Activity-based reporting is important to support activity-based costing, which in turn is important to analysing the efficiency with which program activities are carried out. HPFB undertook an activity-based costing exercise in 2007 to support the proposal for updated user fees, and used the results of this analysis to calculate unit costs for a variety of regulatory activities, including submission review.

The available data indicate that the timeliness of submission review has improved for biologics submissions under the new cost recovery framework. However, without analysing the unit costs of submission review and other cost-recovered activities, it is unclear if improvements in timeliness also represent improved efficiencies. In addition to enabling an assessment of the extent to which efficiencies may have been realized under the new cost recovery framework, such analysis would also assist the BP in identifying where future adjustments to the framework may be necessary. As such, it could update the analysis undertaken in 2007 to support adjustments to the cost recovery framework, which showed that cost of reviewing biologics submissions was considerably higher than the cost of reviewing pharmaceutical submissions. The 2011 updates to the cost recovery framework and user fees did not, however, reflect these differences.

HPFB is reviewing its costs, fees, and performance associated with the BP, as per its commitment in the User Fee Proposal and the Regulatory Impact Analysis Statement associated with the Fees in Respect of Drugs and Medical Devices Regulations.
## Management Response and Action Plan

### Evaluation of the Biologics Program 1999-2000 to 2012-2013

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Response</th>
<th>Action Plan</th>
<th>Deliverables</th>
<th>Expected Completion Date</th>
<th>Accountability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Consistent with international trends and its commitment to enhancing transparency and openness under regulatory modernization, Health Canada should further enhance the amount of clinical trial information it makes publicly available, including the results of clinical trials.</td>
<td>Agree</td>
<td>The department has advanced numerous initiatives to deliver on its commitment to make administrative information about clinical trials more accessible such that patients have adequate information to support their health decisions. Since the closing of this evaluation, in May 2013, the Department launched a database of authorized drug clinical trials. The database is a central source of high level information (protocol number, protocol title, drug name, medical condition, study population, authorization date, sponsor name, HC control number, and the start and end date of the clinical trial, if known) about Phase I, II and III clinical trials in patients. Between April 1, 2013 and October 22, 2013, 328 trials were posted by the Department. The database helps fill an existing information gap revealed by a 2011 survey of international registries that only 24% of clinical trials authorized by HC are publically registered, and of clinical trials in patients, only about 50% were registered. In addition, HC published Clinical Trials Application Guidance for Sponsors. HC also worked with the Canadian General Standards Board (CGSB) to create a new voluntary standard for Research Ethics Boards (REBs), encouraging REBs to make their Standard Operating Procedures publicly available. This standard is available through the Public Works and Government Services Canada website, at <a href="http://www.tpsgc-pwgsc.gc.ca/ongc-cgsc/publications/nouvelles-news/nmcvcb-ncsreo-eng.html">http://www.tpsgc-pwgsc.gc.ca/ongc-cgsc/publications/nouvelles-news/nmcvcb-ncsreo-eng.html</a>.</td>
<td>1.1. TPD is developing a plan which will outline potential future enhancements to the database.</td>
<td>June 2014</td>
<td>DG - TPD</td>
</tr>
</tbody>
</table>

DG - BGTD
### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Response</th>
<th>Action Plan</th>
<th>Deliverables</th>
<th>Expected Completion Date</th>
<th>Accountability</th>
</tr>
</thead>
</table>
| 2. Health Canada should maintain data on the frequency with which On Site Evaluations (OSE) and Lot Release Program (LRP) evaluations identify issues with potential implications for product quality and safety. This information could help to demonstrate the importance of, and need for, these unique components of the BP. | Agree     | The Lot Release Program and the On Site Evaluation function are carried out exclusively by BGTD. For OSEs: BGTD has developed a template, for internal use, that tracks OSEs which have led to either negative submission review outcomes or a significant risk management decision. BGTD commits to maintain this template and to modify it to reflect an assessment of how frequently quality issues identified during a submission review are effectively dealt with during an OSE, and conversely how frequently the OSE process identifies quality issues that are not easily detected via the paper-based review process. The linkage between OSE and positive or negative review outcomes or withdrawn submissions will also be identified. A summary of information will be included in the annual report described below. For Lot Release: BGTD frequently reviews its Lot Release Program to ensure that it remains risk based and as efficient as possible. BGTD commits to produce an aggregate annual summary report on lot release outcomes, beginning with data collected in fiscal year 2014/2015. The report will include the following information:  
- the impact of pre-approval testing on the submission review outcome  
- the number and type of lots released, rejected or withdrawn  
- the estimated level of protection provided to the public via a rejected or withdrawn lot  
- the number of lots changing risk category group  
- the frequency and outcome of use of the lot release program as a specific risk management tool to prevent or alleviate pending or real shortages or stock outs of biologic drugs so that Canadians will continue to have access to these products  

The summary of the OSE information will be included in the report. This report will demonstrate the importance of the program in managing risk throughout the lifetime of biological products. BGTD is known in industry for our collaborative approach to submission review and lot release where we seek to identify and resolve issues early so that they do not become problems to manage (no surprise environment; no surprises in lot release). | 2.1. Aggregate Annual report on the OSE and lot release programs will be produced using 2014/2015 data. | June 2015 and subsequent years | DG - BGTD  |
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Response</th>
<th>Action Plan</th>
<th>Deliverables</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Health Canada should improve its information systems for post-market surveillance and monitoring. In particular, Health Canada should develop and implement a comprehensive and centralized approach to information management for post-market surveillance activities. This should include a centralized mechanism for tracking signal activities related to biologics, including Health Canada’s response to the recommended actions arising from completed biologics signal assessments.</td>
<td>Agree</td>
<td>In 2008 the government introduced Bill C-51 which included the authority to establish terms and conditions on a licence to sell a drug. The compulsory provision of Risk Management Plans (RMPs) and Periodic Safety Update Reports (PSURs) would have been supported by these provisions however the bill died on the order paper with the election call in 2008. In 2009 Health Canada adopted ICH E2E: Pharmacovigilance Planning and instituted processes to facilitate the voluntary submission of risk management plans. At that time, the Department also committed to developing an enabling pharmacovigilance framework through regulatory modernization which would support full implementation of risk management planning. In 2011, Health Canada amended the Food and Drug Regulations(FDR) to require manufacturers to prepare an annual summary report of all information relating to adverse drug reactions and serious adverse drugs reaction, and to notify the Minister of any significant safety changes identified in that report. The Minister can request a copy of the annual summary report and asks that it be submitted in accordance with ICH standards for PSURs. Outside of these requirements Health Canada only receives PSURs on a voluntary basis. New authorities are needed to further compel manufacturers to submit PSURs more routinely as a condition of market authorization. On December 6, 2013, the Minister of Health tabled legislation in Parliament which proposed amendments to the Food and Drugs Act including a requirement for healthcare institutions to report serious adverse drug reactions. Health Canada will work with provinces and territories to create an efficient new reporting system by building on existing systems and best practices. This legislation also includes proposed new regulatory authorities to enable terms and conditions on authorized products for post-market requirements, such as Risk Management Plans. These terms and conditions, if not complied with, will be subject to the new fines and penalties for therapeutic products. Tabling in Parliament, patient safety legislation which includes enabling regulatory authorities to compel post market safety data, such as risk management plans and periodic safety update reports.</td>
<td>In order to ensure robust post-market surveillance and monitoring information systems, the Health Products and Food Branch will develop a proposal on requirements relating to: • improvement of existing tools; • creation of new tools; • creation of partnerships to leverage data from external stakeholders including international regulators, industry and provincial partners such as health care institutions.</td>
</tr>
</tbody>
</table>

| 3.1 The requirements for improvements to existing tools will be brought forward to the department for consideration. | February 2014 |
| 3.2 The requirements for new tools will be brought forward to the department for consideration. | December 2014 |
Currently, Health Canada is implementing electronic reporting of adverse reactions for industry and clinical trial sponsors. The reporting will include post-market and clinical trial adverse reaction information in accordance with international and Health Canada standards and will improve the department’s ability to actively assess trends in pharmaceutical and human drugs adverse reactions both domestically and internationally. This will constitute one of the tools that will contribute to more pro-active surveillance of post-market safety issues. The department continues to improve its strategies to monitor adverse reaction reports through targeted surveillance and improved data-mining (statistical analysis) techniques. Targeted surveillance in this context refers to focusing surveillance efforts on areas that have been identified as being high-risk, based on the identification of a potential safety issue through signal assessments and adverse reaction reports received.

The Health Canada Vigilance Framework (available on the department website) identifies a number of targeted monitoring strategies for:

- **Health product and targeted medical events (HP-TME):** monitoring of specific health product and adverse reaction where a potential safety issue has been noted but more information is needed for confirmation;
- **Designated Medical Events (DME):** monitoring for reports of specific adverse reactions that are often health-product related and potentially disabling or life-threatening such as serious skin reactions or liver failure;
- **New Active Substances (NAS):** monitoring of health products with an active ingredient that has not been previously marketed in Canada.

The targeted surveillance and data-mining initiatives are relatively recent and still in progress. The Department is developing a plan for ongoing improvements to these strategies; this is a significant element in the transition from passive to a more pro-active surveillance approach.
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Response</th>
<th>Action Plan</th>
<th>Deliverables</th>
<th>Expected Completion Date</th>
<th>Accountability</th>
</tr>
</thead>
</table>
| 4. Health Canada should examine whether there is an ongoing rationale for pursuing the authority to compel manufacturers to submit risk management plans as per its commitment under the Food and Consumer Safety Action Plan | Agree | In 2008 the government introduced Bill C-51 which included the authority to establish terms and conditions on a licence to sell a drug. The compulsory provision of Risk Management Plans (RMPs) and Periodic Safety Update Reports (PSURs) would have been supported by these provisions however the bill died on the order paper with the election call in 2008. In 2009 Health Canada adopted ICH E2E: Pharmacovigilance Planning and instituted processes to facilitate the voluntary submission of risk management plans. At that time, the Department also committed to developing an enabling pharmacovigilance framework through regulatory modernization which would support full implementation of risk management planning. In 2011, Health Canada amended the Food and Drug Regulations (FDR) to require manufacturers to prepare an annual summary report of all information relating to adverse drug reactions and serious adverse drug reactions, and to notify the Minister of any significant safety changes identified in that report. The Minister can request a copy of the annual summary report and asks that it be submitted in accordance with ICH standards for PSURs. Outside of these requirements Health Canada only receives PSURs on a voluntary basis. New authorities are needed to further compel manufacturers to submit PSURs more routinely as a condition of market authorization. In the October 2013 Speech from the Throne, the Government committed to introducing new patient safety legislation to help identify potentially dangerous drugs. On December 6, 2013, the Minister of Health tabled legislation in Parliament which provides new regulatory authorities to enable terms and conditions on authorized products for post-market requirements, such as Risk Management Plans. These terms and conditions, if not complied with, will be subject to the new fines and penalties for therapeutic products. Regulatory modernization will define the frameworks under which these products will be regulated including the implementation of the life-cycle approach and the proposed new authorities from Bill C-17. The proposed amendments to the Food and Drugs Act include the power to impose terms or conditions on licenses and authorizations. | 4.1. Tabling in Parliament patient safety legislation which includes enabling regulatory authorities to compel post market safety data, such as risk management plans and periodic safety update reports. | December 2013 (Completed) | DG - MHPD  
DG - PPIAD |
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Response</th>
<th>Action Plan</th>
<th>Deliverables</th>
<th>Expected Completion Date</th>
<th>Accountability</th>
</tr>
</thead>
</table>
| 5. Health Canada should build on its current approach to compliance reporting by increasing its emphasis on compliance and enforcement outcomes, and enhancing its ability to report biologics-specific GMP, GVP, and GCP inspection and compliance data. | Agree     | Health Canada (HC) currently uses the overall compliance rating (i.e. % compliance) of industry as an outcome based performance indicator to measure and assess the results of the Inspectorate’s outputs (i.e. inspection targets, # of incidents opened/closed etc.) in achieving program objectives. This performance measure is reported on monthly and included in the HC Dashboard, as well as used in the Departmental Performance Report (DPR), Report on Plans and Priorities (RPP) and Performance Measurement Framework (PMF). Since the period reviewed in this evaluation, HC has also developed an Annual Inspection summary report for external publication. The report describes in detail the overall compliance rate of industry per program and lists the common observations cited in non-compliant establishments. It also provides specific examples of observations cited against the Food and Drugs Act and Regulations and provides links between inspections conducted by activity (i.e. manufacturer, importer, distributor, etc.), observations noted and their associated risk category. The aim of publishing this report is to address many of the performance outcomes in the PMF, including “Increased awareness and understanding among industry of Health Canada’s regulatory framework”, and “Increased industry compliance with Health Canada’s regulatory requirements. | 5.1. Annual inspection summary report was published on March 31, 2014. - Here is the hyperlink to the "Final English version of the Annual Inspection Summary Report" which was posted on the "Compliance & Enforcement" section of What's New of the Health Canada's Web site: - Inspectorate Program: Annual Inspection Summary Report 2012-2013 [2014-03-31] - The intent is to publish this report on an annual basis. | March 2014               | DG - HPFB Inspectorate
1.0 Introduction

The Biologics Program (BP) is managed through the Health Products and Food Branch (HPFB) of Health Canada. The main program partners involved in delivering the BP are the Biologics and Genetic Therapies Directorate (BGTD), the Therapeutic Products Directorate (TPD), the Marketed Health Products Directorate (MHPD), the HPFB Inspectorate (the Inspectorate), the Regions and Programs Bureau (RAPB), the Policy, Planning, and International Affairs Directorate (PPIAD), and the Resource Management and Operations Directorate (RMOD). Program activities include creating and maintaining the regulatory framework, interacting and communicating with partners and stakeholders, performing risk-benefit assessments, conducting post-market monitoring and surveillance, and compliance and enforcement.

The evaluation of the BP is part of Health Canada’s Five-Year Evaluation Plan. In accordance with the Treasury Board Policy on Evaluation (TBS, 2009), the evaluation assessed the relevance and performance (effectiveness, efficiency, and economy) of Health Canada’s activities under the program. The evaluation covered the period from 1999 to the end of calendar year 2012, with an emphasis on the last five years, although the report also reflects program activities up to the end of December 2013. The results of the evaluation will inform the implementation of current and future program activities.

An independent evaluation consulting firm conducted the evaluation on behalf of Health Canada. The evaluations drew on several lines of evidence, including literature review, document review, review of administrative data, case studies, surveys of manufacturers and other stakeholders, key informant interviews with external and internal stakeholders, and a focus group with cell, tissue, and organ (CTO) establishments. This report presents the evaluation findings, draws conclusions, and makes recommendations.

1.1 Organization of the report

The report is divided into several sections. Section 2 provides a profile of the BP, and Section 3 describes the evaluation methodology. Sections 4 through 7 provide the evaluation findings pertaining to relevance, governance and implementation, achievement of outcomes, and efficiency and economy. Section 8 concludes and presents recommendations. Three appendices accompany the main report. Appendix A contains the evaluation matrix; Appendix B contains the list of references and Appendix C contains supplementary data tables.

2.0 Profile of the Biologics Program

The BP regulates drugs and products derived from living sources, as well as radiopharmaceuticals. Products derived from living sources include blood and blood components and products; vaccines; hormones; enzymes; cytokines; monoclonal antibodies; gene therapy products; cells, tissues, and organs; xenografts; and semen for assisted conception.
The BGTD, as a partner in the Medical Devices Program, is also involved in reviewing combination products (i.e., products that have both a medical device and a biologic component) through joint reviews with the Medical Devices Bureau of the TPD. An example of a combination biologic-device would be tissue-engineered products containing living cells or blood components and cellular products manufactured and sold with a device; a more specific example is an autologous cell therapy product processed with a device to treat cardiovascular disease. Additionally, the BGTD is involved in reviewing devices that are intended to inactivate pathogens in blood components.

The BP operates under the authority of the Food and Drugs Act and Regulations, the User Fees Act, the Safety of Human Cells, Tissues and Organs for Transplantation Regulations, the Processing and Distribution of Semen for Assisted Conception Regulations, the Fees in Respect of Drugs and Medical Devices Regulations, and the Medical Devices Regulations (with respect to combination products). In addition, responsibility for administration of the Assisted Human Reproduction Act (AHRA) was transferred to BGTD in 2012.

The ultimate objective of the BP is to assure “that Canadians have timely access to safe, effective and high quality biologics, as well as the appropriate information about their risks and benefits” (Health Canada, 2012d, p. 3).

2.1 Roles and responsibilities of program partners

The main partners in the BP are the BGTD, the TPD, the MHPD, the Inspectorate, and RAPB. Other partners involved in program delivery and/or management include PPIAD and RMOD. These organizations did not exist at the beginning of the evaluation time period (1999). With the exception of RMOD, which was created more recently, these organizations were announced in the realignment of the former Health Protection Branch in 2000. The roles and responsibilities of each of these partners are briefly described below.

2.1.1 BGTD

The BGTD was established in 2001 as a result of the realignment of the former Health Protection Branch. It is responsible for regulating biologics under the authority of the Food and Drugs Act and Regulations, the Assisted Human Reproduction Act (AHRA), the Safety of Human Cells, Tissues and Organs for Transplantation Regulations, and the Processing and Distribution of Semen for Assisted Conception Regulations. It also has responsibilities in relation to combination products under the Medical Devices Regulations. More specifically, BGTD is responsible for the following:

- developing new regulations, policies, guidance, and Standard Operating Procedures (SOPs), and maintaining/updating existing documents
- conducting pre-market review of product submissions to determine safety, efficacy, and quality of these products, and the appropriateness of their labelling, as well as authorizing their sale in Canada

---

1 The regulation of combination products is beyond the scope of this evaluation but is discussed in detail in the evaluation of the Medical Devices Program, which can be found on the Health Canada website.
• reviewing CTAs, ensuring that there is proper design of the trials and the trials do not pose undue risks to participants, and conducting surveillance of adverse reactions in clinical trials
• evaluating post-market adverse events, complaints, and reports of problems (including performing Health Risk Assessments [HRAs]) to support the post-market activities of the MHPD and the Inspectorate
• reviewing information that product manufacturers provide health care practitioners and consumers about products (e.g., product monographs and package inserts)
• providing science-based information about these products to the Canadian public
• conducting research on methods, tools, and science through participation in peer-reviewed research, academic collaborations, and collaborative work with researchers and regulators nationally and internationally
• conducting on-site evaluations of biologic product manufacturing facilities
• conducting laboratory analyses to support Inspectorate investigations
• overseeing the blood establishments (i.e., establishments that manufacture, collect, or distribute blood and blood components for transfusion and plasma for further manufacturing)
• managing the Lot Release Program, which evaluates biologics at pre-market and post-market stages; each lot of a Schedule D from the *Food and Drug Regulations* (biologic) drug is subject to the Lot Release Program before sale in Canada under the provisions of the *Food and Drug Regulations*.

As of December 31, 2013, the end date for this evaluation and for data collection, the BGTD consisted of three centres, four offices, and one unit (Health Canada, 2012d).2 The three centres are described below (Health Canada, 2011a).

• The Centre for Blood and Tissue Evaluation (CBTE) is responsible for blood and blood components, coagulation factors, immune globulins and other plasma derivatives and their recombinant analogues, cells and cell-based medicines, tissues and organs, xenografts, and semen for assisted conception. In addition, the CBTE evaluates the safety and clinical data for these products.

• The Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB) is responsible for radiopharmaceuticals, hormones, cytokines, enzymes, gene therapies, monoclonal antibodies, and allergenic extracts. In addition, the CERB evaluates the safety and clinical data for these products and for products in CVE.

• The Centre for Vaccine Evaluation (CVE) is responsible for viral vaccines, bacterial vaccines, and combination vaccines. In addition, the CVE conducts regulatory scientific research supporting areas such as vaccines, subsequent entry biologics (SEBs), shelf life and sustainability of biologics, and emerging issues (e.g., stem cells, nano-scale drug delivery systems).

---

2 On January 15, 2014, the CBTE and the CVE were combined to form the Centre for Biologics Evaluation.
Centre responsibilities include review and evaluation of biologics submissions to assure safety, efficacy and quality before they enter the market; laboratory testing to analyse and conduct research on products; and On-Site Evaluations (OSE) to assess manufacturing facilities. The centres also monitor release of biologic products into the Canadian market through the Lot Release Program. The centres collaborate on safety issues related to their products through partnerships and international networks.

BGTD operates one of Health Canada’s Official Medicines Control Laboratories (OMCL)\(^3\), which are used to support the department’s regulatory authorities and national inspection services for marketed health products (Health Canada, 2002).\(^4\) Each centre contains various regulatory divisions which perform lab activities specific to their associated product lines, including pre-market product testing and post-market testing through the Lot Release Program; in addition, as noted above, the CVE’s laboratory conducts regulatory scientific research. Table 1 below lists these regulatory divisions and the types of activities undertaken by the labs.

### Table 1: BGTD laboratory activities

<table>
<thead>
<tr>
<th>Centre</th>
<th>Divisions with laboratory activities</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBTE</td>
<td>• Blood products</td>
<td>• Carry out pre-market product testing to ensure consistency of manufacturing</td>
</tr>
<tr>
<td>CERB</td>
<td>• Hormones and enzymes</td>
<td>• Perform post-market biologic testing through the lot release program</td>
</tr>
<tr>
<td></td>
<td>• Monoclonal antibodies</td>
<td>• Conduct regulatory scientific research (CVE only)</td>
</tr>
<tr>
<td></td>
<td>• Cytokines</td>
<td></td>
</tr>
<tr>
<td>CVE</td>
<td>• Viral vaccines(^*)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bacterial and combination vaccines(^*)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Biological analysis laboratories</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Genomics laboratories</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Protein structure and analysis laboratories</td>
<td></td>
</tr>
</tbody>
</table>

Source: (BGTD, 2010a, 2011c)

\(^*\) As of 2011, the CERB was responsible for evaluating the safety and clinical data for viral vaccines and bacterial and combination vaccines (BGTD, 2011c)

The other entities within the BGTD are described below.

- The Office of Policy and International Collaboration is responsible for partnering with the three centres to develop and update policies, standards, guidelines, and other legislative instruments for biologics and radiopharmaceuticals. It also engages in stakeholder consultations, coordinates international collaboration activities, and undertakes cost-benefit analyses and project evaluations.

- The Office of Regulatory Affairs is responsible for management of submissions for biologics and radiopharmaceuticals, conducting activities such as screening/validation, coordination of submission meetings with industry, managing regulatory correspondence, developing submission review performance reports, and entering data for all adverse drug reactions related to biological clinical trials.

---

\(^3\) The other OMCL are operated by the Inspectorate (BGTD, 2010a).

\(^4\) The OMCL originated in Europe in the mid 1990s and is coordinated by the European Directorate for the Quality of Medicines and Healthcare (EDQM) (Health Canada, 2002).
• The Office of Quality and Information Management manages the BGTD-wide quality management system (QMS), performing activities such as internal quality system audits, management reviews, analysing QMS performance data, administering QMS databases, coaching process improvement, coordinating the QMS training program, and developing/implementing the information management approach used by the BGTD.

• The Office of Business Integration and Risk Management is responsible for coordinating risk management for the BGTD, conducting activities such as coordination of the BGTD emergency preparedness and business continuity activities, briefing and correspondence for the BGTD, coordination of review panels and requests for reconsideration for submissions. Other activities conducted by this group include the implementation of strategic initiatives and broad projects, operational planning, and performance measurement.

• The Administrative Services Unit is responsible for providing administrative support and guidance to BGTD management and staff.

2.1.2 TPD

The Therapeutic Products Directorate (TPD) is responsible for regulating pharmaceuticals for human use under the authority of the Food and Drugs Act and Regulations. As a partner in the BP, the TPD, through the Office of Submissions and Intellectual Property (OSIP), receives biologic drug submissions; maintains the Drug Submission Tracking System; and produces quarterly and annual biologic drug submission reports on behalf of BGTD. TPD also prepares Summary Basis of Decision (SBD) documents on behalf of BGTD, and gives access to both non-marketed biologics and pharmaceutical drugs through the Special Access Program when conventional therapies have failed, or are unsuitable or unavailable.

2.1.3 MHPD

The MHPD works to assure that HPFB programs take a consistent approach to post-approval safety surveillance, assessment of safety signals and trends, and risk communications concerning all regulated marketed health products (Health Canada, 2012h). Responsibilities relevant to biologics include the following:

• monitoring a variety of sources for safety signals, including Periodic Safety Update Reports (PSURs), Periodic Benefit Risk Evaluation Reports (PBRERs) and other information provided by market authorization holders (MAHs), as well as international data
• managing the Canada Vigilance Program, Health Canada’s post-market surveillance program that collects and assesses reports of suspected adverse reactions to health products marketed in Canada, and monitoring adverse reaction and medication incident data collected through the program
• conducting comprehensive safety assessments, such as signal assessments, benefit-risk assessments and reviews for Risk Management Plans (RMPs) for marketed health products, as well as reviews for RMPs for certain health products submitted for authorization
monitoring regulatory advertising activities
communicating health product risks to the public and health care practitioners
developing policies and strategies for post-market surveillance.

2.1.4 Inspectorate and RAPB

The main role of the Inspectorate is “to deliver a national compliance and enforcement program for all products under the mandate of the Branch, with the exception of food products that are the responsibility of the Canadian Food Inspection Agency” (Inspectorate, 2011). With respect to biologics, the Inspectorate carries out the following activities:

- developing policy related to compliance and enforcement of regulations
- licensing drug establishments that are compliant with regulatory requirements and amending, suspending, or refusing to issue Establishment Licences (ELs) when non-compliances are found
- conducting monitoring inspections of drug establishments to verify compliance with regulatory requirements for Good Manufacturing Practices (GMPs)
- conducting inspections of clinical trial sites in Canada for Good Clinical Practices (GCPs)
- conducting inspections of establishments for Good Pharmacovigilance Practices (GVPs) for post market reporting of adverse drug reactions
- conducting inspections of blood and blood components, semen for assisted conception, and CTO establishments for compliance with regulatory requirements
- registering CTO establishments
- conducting compliance verifications in response to specific complaints or identified risks relevant to biologics and clinical trials of biologics
- providing chemical, physical, and microbiological analysis services through the Laboratory Program to support inspection and investigation activities
- conducting compliance promotion activities with industry stakeholders.

RAPB is the operational arm of Health Canada in the regions. Responsibilities include compliance promotion activities, as well as enforcement of laws and regulations through inspections, investigations, legal action, and evaluations of compliance with standards affecting manufacturing, packaging and labelling, analysis, importing, distributing, and wholesaling of health products.

2.1.5 Other partners

Two other Health Canada partners also have responsibilities under the BP.

- PPIAD provides leadership and support on strategic planning, as well as policy development and planning on horizontal issues of strategic importance. It also provides leadership with respect to international affairs.
- RMOD is responsible for resource allocation, including cost recovery policy and implementation, as well as rolling up performance measurement information to generate

---

5 It is important to note that the GMP, GCP, and GVP inspection programs encompass both pharmaceutical and biologic drug products.
Branch and Departmental performance reports. These responsibilities were transferred to RMOD from PPIAD in July 2011.

2.2 Program activities and logic

The BP consists of five main activities delivered by the program partners:

- development and implementation of the regulatory framework
- communication and stakeholder engagement
- risk and benefit assessments related to clinical trial authorization and market authorization
- post-market surveillance and monitoring
- compliance and enforcement of the regulatory framework.

These activities correspond with specific immediate, intermediate, and long-term outcomes. In the immediate term, program activities are expected to lead to increased external stakeholder awareness and understanding of risks and benefits related to biologics. They are also expected to improve industry awareness and understanding of Health Canada’s regulatory framework for these products, to enhance the safety and effectiveness of these products, and to increase industry compliance with the relevant regulatory framework.

The achievement of these immediate outcomes is expected to lead to intermediate outcomes of external stakeholder adoption of safe behaviours associated with biologics; increased use of scientific evidence and risk-benefit analysis by Health Canada to inform decision making; timely regulatory response to identified risks; reduced exposure to health risks associated with the use of these products; and harmonization of Canada’s regulatory framework with international approaches.

In the long term, Health Canada expects to reduce adverse events associated with the use of biologics; increase public confidence in biologics and the related regulatory system; and produce a sustainable, cost-efficient, responsive, and science-based regulatory system for these products in Canada.

A logic model that depicts the linkages between the activities, outputs, and expected outcomes of the BP is describe below in (Section 2.2.1).

2.2.1 Description of the Logic Model

The BP uses the following resources (inputs) to deliver its activities, produce outputs and accomplish its outcomes: funding; human resources; facilities, infrastructure; Acts, regulations, policies and priorities; science and technology; and, research data.

The BP consists of five main activities delivered by the Program partners, namely:

- development, implementation and maintenance of the regulatory framework for biologic products
- communication with partners and stakeholders

To obtain a copy of the Logic Model graphic please use the following e-mail “Evaluation Reports HC - Rapports Evaluation@hc-sc.gc.ca”.

May 2014 7
• risk and benefit assessments of biologic and radiopharmaceutical products
• post-market surveillance and monitoring for biologic products’ safety and effectiveness
• compliance and enforcement

These activities are targeted at different groups, namely:

• development, implementation and maintenance of the regulatory framework for biologic products
  • Canadian public; consumer associations; Federal/Provincial/Territorial (F/P/T) governments and Other Government Departments (OGDs); health care professionals; industry; industry/professional associations; international governments/organizations; media; and, researchers
• communication with partners and stakeholders
  • Canadian public; consumer associations; F/P/T governments and OGDs; health care professionals; industry; industry/professional associations; international governments/organizations; media; and, researchers
• risk and benefit assessments of biologic and radiopharmaceutical products
  • F/P/T governments; health care professionals; industry; international governments/organizations; and, researchers
• post-market surveillance and monitoring for biologic products’ safety and effectiveness
  • Canadian public; Health Canada regulators; clinical community; MAHs; and, international governments/organizations
• compliance and enforcement
  • Canadian public; F/P/T governments/OGDs; Health Canada regulators; industry; and, international governments/organizations

As a result of each activity, the Program generates a number of products and/or services, namely:

• development, implementation and maintenance of the regulatory framework for biologic products
  • legislation and regulations; policies; guidance; Mutual Recognition Agreements; Memoranda of Understanding; Treasury Board submissions and Memoranda to Cabinet; and, research findings/papers
• communication with partners and stakeholders
  • data sources/systems, Web sites; stakeholder educational material/events/meetings; publications, notifications, advisories; correspondence/public enquiries; and, SBDs
• risk and benefit assessments of biologic and radiopharmaceutical products
• Clinical Trial Authorizations; product submissions; establishment licences; risk-benefit assessments (initial and on-going, including HRAs); Special Access Program; and, Special Access Program decisions (seminars), PSURs, notifiable changes, licence amendments
• post-market surveillance and monitoring for biologic products’ safety and effectiveness
• Canada Vigilance Program; data, analysis, evidence; reports, regulatory recommendations; signal identification and characterization; science reviews and input into the Drug Safety and Effectiveness Network; and, Risk Management and Mitigation Plans
• compliance and enforcement
• compliance and enforcement reports; compliance and enforcement actions, including prosecution and public warnings, licence suspension, seizures, stop sales and search, etc.; Risk Management and Mitigation Plans; and, investigation reports

The implementation of the activities identified above corresponds with specific immediate, intermediate and long-term outcomes. In the immediate term, the development, implementation and maintenance of the regulatory framework for biologic products as well as communication with partners and stakeholders are expected to lead to increased external stakeholder awareness and understanding of risks and benefits related to biologic products as well as to increased industry awareness and understanding of Health Canada’s regulatory framework for biologic products. This latter outcome together with compliance and enforcement activities are expected to increase industry compliance with Health Canada’s regulatory requirements related to biologic products. Similarly, conducting risk and benefit assessments together with post-market surveillance and monitoring activities are expected to increase the safety and effectiveness of biologic products.

The achievement of these immediate outcomes is expected to lead to the achievement of intermediate outcomes. In this manner, increased external stakeholder awareness and understanding of risks and benefits related to biologic products as well as increased industry awareness and understanding of Health Canada’s regulatory framework for biologic products are expected to lead to a harmonization of Canada’s regulatory framework for biologic products with international approaches. Increased external stakeholder awareness and understanding of risks and benefits related to biologic products is also expected to lead to external stakeholder adoption of safe behaviours associated with biologic products.

Increased safety and effectiveness of biologic products is expected to lead to increased use of scientific evidence/risk-benefit analysis by Health Canada to inform decision making and timely regulatory response to identified risks. Increased use of scientific evidence/risk-benefit analysis feeds into timely regulatory response, which together with external stakeholder adoption of safe behaviours, increased safety and effectiveness of biologic products and increased industry compliance are expected to lead to a reduced exposure to health risks associated with biologic products.
In the long term, intermediate outcomes of external stakeholder adoption of safe behaviours associated with biologic products, increased use of scientific evidence/risk-benefit analysis by Health Canada to inform decision making, timely regulatory response to identified risks, and a reduced exposure to health risks associated with biologic products are expected to contribute to a reduction of adverse events associated with the use of biologic products, increased public confidence in biologic products (and related regulatory system and programs), and to a sustainable, cost-efficient, responsive, and science-based regulatory system for biologic products in Canada. This latter outcome is also influenced by the harmonization of Canada’s regulatory framework for biologic products with international approaches.

The ultimate outcome of the Program is to help ensure access to safe and effective biologic products and to provide information for healthy choices.

### 2.3 Resources

The BP is funded by appropriations, targeted funding and revenues through cost recovery. In 2011–2012, total BP expenditures were $54.4 million. Revenues from cost recovery were $6.0 million.

### 2.4 Program context

Management and delivery of the BP, like all federal regulatory programs, is influenced by a number of overarching policies, directives, and pieces of legislation, which provide context for such programs. Regulations are one of a number of government instruments to achieve policy outcomes. The 2012 Cabinet Directive on Regulatory Management requires regulatory programs to demonstrate efficiency and effectiveness by ensuring that the benefits of regulation justify the costs and by demonstrating tangible results for Canadians (GoC, 2012b). Inherent in the Directive is the need to consult with affected bodies at all stages of the regulatory process; to select the appropriate mix of government instruments, including regulatory and non-regulatory responses; to impose the lowest-possible cost on businesses and Canadians that is necessary to achieve the policy objectives; to take advantage of opportunities for coordination and collaboration with provincial/territorial governments and internationally, including limiting the number of specific Canadian regulatory requirements and minimizing differences with key trading partners (i.e., the US); and to measure and report to Canadians in a timely manner on the performance of regulatory programs.

In May 2012, HPFB released the Regulatory Roadmap for Health Products and Food (Health Canada, 2012k). The Roadmap envisions an efficient and transparent regulatory system that protects and improves consumer safety, reduces regulatory burden for small business, supports scientific innovation, and increases the variety of health options and benefits available to Canadians. These goals are consistent with the Cabinet Directive on Regulatory Management, which requires federal departments to consider the impact on small businesses of new or amended regulations, while protecting and advancing the public interest in health and safety. These goals are also guided by the Government of Canada’s Red Tape Reduction Action Plan, which aims to reduce administrative burden on business.
Regulatory programs that impose a user fee, such as the BP, are subject to the User Fees Act (GoC, 2004). The Act requires regulating authorities to consult with clients and service users and establish service standards comparable to those in other countries prior to amending fees or creating new ones.

The Communications Policy of the Government of Canada requires federal institutions to, among other things, provide the public with “timely, accurate, clear, objective and complete” information about policies, programs, services, and initiatives in all regions of Canada and in a range of formats, and to consult the public when establishing priorities and planning programs and services (GoC, 2012c).

3.0 Evaluation methodology

This section of the report describes the evaluation methodology.

3.1 Evaluation design and methods

The evaluation design was developed based on the findings of an evaluability assessment completed as a first step in the evaluation. The evaluability assessment consisted of a preliminary review and assessment of available documents and administrative data.

The evaluation design and the evaluation matrix (Appendix A) were developed based on the evaluability assessment. The evaluation matrix addresses 10 key questions and a number of sub-questions relating to program relevance and performance (effectiveness, efficiency, and economy), in accordance with the Treasury Board Policy on Evaluation (2009).

The evaluation consisted of several data collection methods. Some of the data collection methods, in particular the survey of stakeholders, the external key informant interviews, the case studies, and the administrative data review, were designed to capture information to support one or both of two concurrent evaluations of other HPFB regulatory programs, namely, the Human Drugs Program (HDP) and the Medical Devices Program.

**Literature review.** The literature review addressed evaluation questions related to program relevance, long-term outcomes, and alternate approaches. Peer-reviewed (i.e., scientific and academic) and grey literature was considered in the review. Relevant literature was located through online searches.

**Document review.** The document review addressed all of the evaluation questions to the extent that supporting documents were available. The reviews encompassed government documents, primarily produced by Health Canada, related to BP planning, management, and ongoing operations. Several thousand documents were reviewed as part of the evaluations.
Administrative data review. The administrative data review addressed evaluation questions related to program outcomes. The review considered data produced by the BGTD, the TPD, the MHPD, and the Inspectorate. Although theoretically distinct, the document review and the administrative data review were, in practice, two aspects of the same task, as the majority of administrative data was included in program documents.

To support the literature, document, and administrative data reviews, a library was developed of approximately 3,500 individual documents, sources of administrative data, and pieces of literature, including approximately 1,650 documents; 980 web pages; 570 journal articles; and various other types of sources, which were reviewed over the course of the evaluation.  

Case studies. Three case studies were conducted to support the BP evaluation, focusing on genetic therapies, SEBs, and contamination of biologic products. In addition, a case study was completed that examined Health Canada’s signal detection, signal assessment, and risk management activities for both biologics and pharmaceutical drugs, and was used to inform both evaluations. Finally, as part of the HDP evaluation, a case study was completed that focused on Health Canada’s approach to clinical trials. Although completed in the context of the HDP evaluation, because the same regulatory framework applies to biologics as well as pharmaceutical drugs, the clinical trials case study was also used to inform the evaluation of the BP.

Survey of industry. The bilingual survey of industry used a web-based approach and focused on evaluation questions related to outcomes. Guidance and direction from Public Works and Government Services Canada on public opinion research and surveys limited the evaluation to surveying individuals who were known to have had contact with Health Canada for reasons related to the BP. Initially, the scope was to include all manufacturers currently licensed to manufacture biologics in Canada (which was the approach taken in the evaluation of the Medical Devices Program). Instead, the sample was drawn by Health Canada from the Department’s Stakeholder Information Management System (SIMS) database and the Drug Product Database (DPD).

After cleaning, the final sample for the biologics industry survey consisted of 227 manufacturers. These 227 manufacturers included those who produced any type of biologic, regardless of whether they also produced additional products, such as human pharmaceutical drugs.

The biologics industry survey achieved 19 completions, representing a completion rate of 10.3%. Although a 10% response rate is not uncommon for web-based surveys of industry, these response rates are lower than anticipated and may be due to the fact that an initial communication was not sent by Health Canada to potential respondents. Instead, the survey invitation was disseminated by the consulting firm.

Survey of other stakeholders. A bilingual web-based survey was also used to reach users of biologics, including health care professionals and patient/consumer organizations. This survey was also intended to capture outcome information from users of human pharmaceutical and biologic drugs and medical devices to support concurrent evaluations of Health Canada’s
regulatory activities in those areas. In particular, the survey was intended to capture information on the impact of Health Canada’s communication and consultation activities on stakeholder awareness and understanding of risks related to therapeutic products, as well as information on the impact of these activities on stakeholder use of these products.

As was also the case with the industry survey, the evaluation was limited to surveying individuals who were known to have had contact with Health Canada. Accordingly, the evaluation requested to use Health Canada’s MedEffect listserv, which consists of over 20,000 subscribers to MedEffect’s e-notice, as the survey sample. In light of concerns about privacy, the possibility that use of the listserv for survey purposes might cause subscribers to unsubscribe to MedEffect, and the fact that the listserv includes individuals who are not within the survey’s target group (such as Health Canada employees and health care professionals and consumers residing outside of Canada), however, the listserv was not made available.

To support the survey, Health Canada provided a list of stakeholders identified by Health Canada through its SIMS database. After cleaning the sample, the final sample consisted of 651 potential respondents.

The questionnaire included separate modules for medical devices, pharmaceutical drugs, and biologics. A total of 16 stakeholders responded to the survey, representing a completion rate of 2.6% overall. Of these, 11 (1.7% of potential respondents) responded to the module relating to biologics. While the reasons for this low response rate are not clear, they may include the lack of an initial communication from Health Canada.

**Focus group with CTO establishments.** As part of the BP evaluation, a focus group with CTO establishments was conducted, which focused on their experiences since implementation of the Safety of Human Cells, Tissues and Organs for Transplantation Regulations in 2007. Focus group participants were recruited from a list of all registered CTO establishments across Canada provided by Health Canada. Efforts were made to ensure participation from establishments in all regions of Canada, with recruiting within each region taking place until the maximum overall number of participants (n=10) were enrolled. In total, nine representatives of CTO establishments participated in the focus group. All participants received an honorarium for their participation, which helped offset the opportunity cost of their participation during regular business hours. The focus group was conducted by telephone.

**External key informant interviews.** The external key informant interviews focused on evaluation questions relating to program implementation and effectiveness. The interviews addressed questions relating to medical devices, pharmaceutical drugs, and biologics in order to support all three evaluations without overburdening key informants with multiple requests for interviews. Interviewees included industry representatives, researchers and academics, patient and consumer organizations, health care providers, professional associations, international key informants, and others.

---

9 Calculated out of 622 valid email addresses.
Overall, a total of 93 potential key informants were identified, and 53 individuals participated in an interview or provided a written response to the interview questions, including 18 who made comments relevant to biologics. Interviews were conducted by telephone in each key informant’s preferred official language. The interviews were recorded to ensure accuracy, and the notes were returned to key informants for review and approval. Key informants were assured of the confidentiality of their responses.

**Internal key informant interviews.** The internal key informant interviews were completed after a draft of the evaluation report had been submitted and were intended to provide an opportunity for representatives of the BP to clarify issues and, to the extent possible, fill gaps in information. A total of 19 individuals, representing BGTD, MHPD, and the Inspectorate, were interviewed using a combination of individual and group interviews. As with the external interviews, the interviews were recorded to ensure accuracy, and the notes were returned to key informants for review and approval. The draft report was revised based on written comments received from the BP, as well as the information obtained through these interviews and discussions.

### 3.2 Reporting

For final reporting, data from all lines of evidence was integrated or triangulated in order to arrive at the overall evaluation findings. Triangulation is a process through which answers to research questions generated by different data collection methods are compared. Where different methods produced similar findings, those findings were assumed to have greater validity, and, therefore, greater confidence in the results is warranted.

### 3.3 Limitations of the methodology and mitigation strategies

There are several important methodological limitations to note. First, given the vast scope and complexity of the subject matter, the document review and the literature review were both limited by the time and resources available to complete them. The document review was further limited to documents that were provided to the evaluation by Health Canada, or that were publicly accessible. These limitations were mitigated by the use of multiple lines of evidence, wherever possible, to produce the evaluation findings.

The stakeholder survey was limited as a direct result of the sample development process. In particular, the sample for the survey was small, especially in comparison to the actual health care provider and patient/consumer populations. Furthermore, for reasons that are not entirely clear, the survey achieved a very low overall response rate (2.6%), and only 11 stakeholders responded to the component pertaining to biologics. While the use of the MedEffect list might not have produced a higher response rate, it would have, at minimum, increased the number of completions to a level worth reporting. Thus, it would have provided some data to support outcome questions relating to the impact of Health Canada’s risk communications on stakeholder awareness,
understanding, and behaviour. In the absence of survey data, there is very little information to support conclusions on these questions. Ultimately, there was no satisfactory mitigation strategy for this limitation, and the evaluation had to rely on somewhat dated public opinion research. It is important to note that Health Canada does not routinely collect this information and that the survey of stakeholders was itself, in the first instance, an attempt to mitigate and address this gap.

Like the stakeholder survey, the industry survey was also limited by a small and unrepresentative sample drawn from the population of manufacturers in Canada, combined with a low response rate. To mitigate this limitation, survey findings are used sparingly throughout this report. When survey results are included, they are treated as qualitative information.

With respect to the external key informant interviews, many of those who chose not to participate (just over 40%) indicated that they were not familiar enough with the program to give meaningful responses. It is unknown if the interview findings would have been substantially different had these individuals participated. Like all key informant data, the findings from the interviews should not be interpreted as representing the views of stakeholders in general; these findings are limited by self-selection bias. The same limitation applies to the findings from the focus group with CTO establishments. To mitigate this limitation, and to the extent possible, information from key informant interviews has been triangulated with other lines of evidence.

Finally, interviews with program representatives were completed after a draft of the final report was prepared. The evaluation would have benefitted from a larger number of interviews with program representatives, conducted earlier in the process.

4.0 Findings – relevance

This section of the report presents the evaluation findings on relevance.

4.1 Ongoing need

There is an ongoing need for continued oversight by Health Canada to help protect the health and safety of Canadians. Increased use of biologics is exposing more Canadians to the risks, as well as the benefits of these products. Health Canada’s role is consistent with federal and Health Canada roles and responsibilities.

---

10 That being said, even if the MedEffect list had been used, the opinions and information collected by the survey would not have represented the general population of stakeholders in Canada. Rather, the opinions and information would have reflected a group of stakeholders who receive frequent communications from Health Canada.
The evaluation confirmed an ongoing need for government oversight of biologics in order to help protect the health and safety of Canadians. Use of these products is growing due to demographic changes such as population growth and aging, as well as marketing by industry. As a result, more Canadians will be exposed to the risks, as well as the benefits, of these products, suggesting a need for continued oversight by Health Canada to manage these risks. Moreover, trends such as the emergence of combination products and globalization of the supply chain are creating uncertainties that further support the need for government intervention to help protect the health and safety of Canadians.

4.1.1 Trends in the use of biologics

Biologics contribute significantly to the health of Canadians and represent an important component of the Canadian health care system. In fact, the use of biologics has been increasing in recent years due to a number of factors. As the pharmaceutical industry has experienced the “patent cliff,” which refers to the loss of patent protection for many of its top-selling brand-name products, it has responded in two ways. First, it has focused on extending patent protection for existing products, as well as developing new pharmaceutical drugs similar to products already in the marketplace (Ferguson & Lybecker, 2012).

Second, it has shifted towards the development of high-cost products, most notably biologics, for less common medical conditions. Indeed, biologics are frequently used in the treatment of rare diseases, which Health Canada defines as life-threatening, seriously debilitating, or serious chronic conditions that only affect a very small number of patients. The drugs used to treat these diseases are called orphan drugs. Development of orphan drugs is occurring primarily within the biologics industry; one source estimates that biologics accounted for approximately 60% of the global orphan drug market in 2006, and over 50% of the leading orphan drugs were biologics (Ariyanchira, 2008).

At the same time, while many biologics are used to treat rare diseases and less common medical conditions, it is also important to note that one of the drivers of the rapid growth in biologics has been the increased approval of biotechnology drugs for more common, long-term conditions such as diabetes, cardiovascular disease, digestive disorders and asthma (Cohen, Morrow, & Penna, 2006). Other drivers of the growth in biologics include increased availability of targets for biologic agents, increased use of approved drugs, and expanded indications for approved drugs (Cohen et al., 2006). Currently, biologics are used in the treatment of a wide range of common conditions, most commonly cancer, acquired immunodeficiency syndrome/human immunodeficiency virus, rheumatoid arthritis, multiple sclerosis, anemia, hepatitis C, transplantation medicine, and complications caused by human growth hormone (Cohen et al., 2006).

In Canada, although some biologics have been used for many years, biologics produced using biotechnology have rapidly achieved acceptance in the marketplace. As shown in Table 2, some of these biologic products are among the top-selling drugs in the country. In 2012, four of the

---

11 Health Canada notes that the small size of the patient population makes it scientifically difficult and often commercially impracticable for drug companies to develop and market orphan drugs; hence the need for specific regulations for the development, evaluation and approval of these drugs (Health Canada, 2013m).
five top-selling drugs in Canada, and five of the top ten, were biologics (Remicade, Enbrel, Humira, Lucentis, and Rituxan). It is important to note that biologics are costly by comparison to pharmaceuticals – in 2012, nine of the 11 most expensive drugs in the US were biologics (Skerrett, 2012) – due to the significant investment in infrastructure and clinical trial programs involved in their production (Scott, 2012). In light of the high costs of biologics and the potential consequences for consumers and reimbursement agencies, the cost-effectiveness of biologics is a matter of ongoing debate and analysis (Sheridan & Katsnelson, 2005; van der Velde et al., 2011).

Table 2: Top-selling drugs in Canada, 2012 (biologics in bold)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Product name</th>
<th>Therapeutic subclass</th>
<th>Total sales ($ millions)</th>
<th>2012 growth (%)</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Remicade</td>
<td>Anti-arthritic</td>
<td>564.84</td>
<td>2.6</td>
<td>Schering</td>
</tr>
<tr>
<td>2</td>
<td>Crestor</td>
<td>Cholesterol Reducer</td>
<td>411.6</td>
<td>1.9</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>3</td>
<td>Humira</td>
<td>Anti-arthritic</td>
<td>373.5</td>
<td>1.7</td>
<td>Nycomed</td>
</tr>
<tr>
<td>4</td>
<td>Enbrel</td>
<td>Anti-arthritic</td>
<td>315.8</td>
<td>1.4</td>
<td>Amgen</td>
</tr>
<tr>
<td>5</td>
<td>Lucentis</td>
<td>Vision loss</td>
<td>286.4</td>
<td>1.4</td>
<td>Novartis</td>
</tr>
<tr>
<td>6</td>
<td>Lyrica</td>
<td>Seizure Disorders</td>
<td>235.8</td>
<td>1.1</td>
<td>Pfizer</td>
</tr>
<tr>
<td>7</td>
<td>Cipralex</td>
<td>Antidepressant</td>
<td>215.2</td>
<td>1.0</td>
<td>Purdue</td>
</tr>
<tr>
<td>8</td>
<td>Nexium</td>
<td>Stomach acid control</td>
<td>210.1</td>
<td>1.0</td>
<td>Astrazeneca</td>
</tr>
<tr>
<td>9</td>
<td>Advair</td>
<td>Asthma Therapy</td>
<td>203.9</td>
<td>0.9</td>
<td>Abbott</td>
</tr>
<tr>
<td>10</td>
<td>Rituxan</td>
<td>Autoimmune</td>
<td>200.0</td>
<td>0.9</td>
<td>Roche</td>
</tr>
</tbody>
</table>

Source: (Industry Canada, 2012)

Several other industry trends are also worth noting. First, new classes of biologic drugs are beginning to emerge. These include second-generation biologics, also known as biobetters or biosuperiors, which are products that have been “structurally and/or functionally altered to achieve an improved or different clinical performance”; “me-too” or “non-innovator” biologics, which have been developed independently and may not have been compared directly against licensed products; and subsequent entry biologics (SEBs), also known as biosimilars, which differ from non-innovator biologics in that they are formally compared with a currently licensed product (Weise et al., 2011, p. 691). With patent protection for many biologic drugs nearing its end, a key emerging issue for regulators involves managing the approval and reimbursement of these classes of biologic drugs.

In addition, the emergence of combination products is creating challenges for regulators around the world. Emerging medical technologies, most notably in regenerative medicine, may combine biologics and devices in a variety of complicated ways (Lee, 2010; von Tigerstrom, 2012). From a regulatory standpoint, this creates challenges in determining which regulations govern the product in question and/or which regulatory body or bodies have authority over its testing, approval, and use. Finally, globalization of the supply chain for therapeutic products is creating challenges for national regulatory agencies in managing risk at various points in the manufacturing process and the product lifecycle, and creating pressure for increased harmonization of regulatory approaches.
4.1.2 Risks associated with biologics

A variety of risks to human health and safety are associated with the use of biologics, implying that some degree of regulatory oversight is necessary in order to manage these risks.

Risks arising from incomplete understanding of a product’s effect on human health

Despite pre-market processes instituted in Canada and other jurisdictions since the 1960s, safety concerns periodically result in approved products being withdrawn from the market. Since 2004 in Canada, there have been 28 brand-name and generic human pharmaceutical and biologic drugs (involving 22 active ingredients) inactivated by the manufacturer for safety reasons (Health Canada, 2013e). Of these, two (Raptiva and Xigris) were biologics.

Biologic drugs and therapies have been linked to a variety of adverse human health impacts. For example, biologic drugs incorporating monoclonal antibodies have been linked to serum sickness, tumour lysis syndrome, cytokine release syndrome, heightened risk of infection, platelet and thrombotic disorders, autoimmune diseases, cancer, dermatitis, and cardiac dysfunction (Hansel, Kropshofer, Singer, Mitchell, & George, 2010).

Similarly, developing biologic therapies, such as cell and gene therapies, also carry certain risks. These may include autoimmune responses, transmission of infectious diseases, introduction of adventitious agents, and alteration of cells’ biological characteristics, causing malignant transformations in cells that result in the formation of tumours. Canada recently issued a Notice of Compliance with Conditions (NOC/c) for Prochymal for use in paediatric patients with graft-versus-host-disease not responding to steroids (Clarke, 2012), making it the first country to approve a stem cell therapy, while the EU recently became the first jurisdiction to approve a gene therapy by granting market authorization to Glybera for the treatment of lipoprotein lipase (LPL) deficiency (Grogan, 2012).12

In the case of orphan drugs such as Prochymal and Glybera – many of which, as already noted, are biologics – there is a greater chance that products may be approved on the basis of an incomplete understanding of their safety profile. This is because the small size of the patient population means that clinical trials are more likely to be conducted with relatively small groups of patients. Consequently, clinical trials may not always provide a complete understanding of the effects of these products on human health, especially over the longer-term. This speaks to the need for ongoing monitoring of individuals treated with biologics and analysis of long-term safety data. For biologics that have been on the market for a number of years, long-term safety data is beginning to emerge and is being analysed to determine the effects of extended exposure to these products (Horton, Nam, & Buch, 2012; Panchal, Coope, McKenna, & Alexandroff, 2014).

---

12 LPL deficiency is a rare autosomal recessive single gene deficiency resulting in the build-up of lipoprotein in the gut wall; this results in numerous complications, including pancreatitis, which can be life-threatening (Flemming, 2012).
Risks arising during manufacturing and distribution

Opportunities for contamination may arise during product manufacturing and distribution if appropriate quality control measures, such as complying with GMPs, are not taken. Contamination may occur due to unintended exposure to physical, chemical, microbial, or other contaminants during product manufacture or distribution. Furthermore, the environmental sensitivity of some biologic drugs renders them particularly vulnerable to physical and chemical degradation as a result of poor manufacturing and distribution practices and/or deliberate diversion from the supply chain. Products affected by degradation may exhibit reduced efficacy and also may present significant safety risks for the end-user.

Counterfeiting of biologics – deliberately substituting bulk process intermediates (BPIs) or excipients with other substances capable of causing serious harm to the end user – does not appear to be a significant problem at this time. However, in one high-profile example in 2008, hundreds of adverse events and potential deaths resulting from allergic-type reactions and hypotension in US patients undergoing dialysis were ultimately traced to adulteration in China of the blood thinner heparin (a biologic, though regulated as a pharmaceutical at the time) with oversulfated chondroitin sulphate (OSCS), a synthetic material with similar chemical properties to heparin but costing one hundred times less than the latter (Pew Health Group, 2011, pp. 16–20).

During the heparin incident, BGTD’s laboratories performed a key role in determining the nature of the heparin contamination. Over a period between March 19 and May 15, 2008, BGTD laboratories tested 168 lots of heparin sodium and low molecular weight heparin products from several manufacturers, requiring approximately 60 days (for one FTE) for sample preparation and data collection, and for data analysis and preparations. Additionally, analyses of heparin, and Chondroitin A and C purchased from Sigma-Aldrich were performed (Health Canada, 2013b, 2013c). On March 19, 2008, Health Canada learned from the FDA that the heparin contaminant was OSCS, and, on the subsequent day, BGTD labs identified the presence of OSCS in product produced by B. Braun Medical Inc. On the same day, Health Canada published an advisory announcing this finding and its intent to work with the manufacturer to recall the affected product from the Canadian market (Health Canada, 2008a). The voluntary recall began on March 21, 2008.

Health Canada notes that in addition to causing direct harm from contaminated or substandard ingredients, poor-quality or counterfeit products may fail to have the necessary therapeutic effect, resulting in patient harm or discomfort; additionally, low-quality ingredients or manufactured health products could promote drug resistance or create shortages if subject to recall (Health Canada, 2012c).

Risk of infectious disease transmission

Some biologic products, including blood and blood components as well as tissues and organs for transplantation, carry a risk of infectious disease transmission. Blood and blood components serve a variety of purposes in Canada, such as treating injuries and diseases (e.g., cancer and blood disorders), as well as facilitating medical interventions (e.g., hip and joint surgeries and

---

13 In 2010–2011 and 2011–2012, the National Border Integrity Program found no instances of counterfeit product among inspected shipments of biologic drugs; see Section 6.4 for more information.
transplant). According to public opinion research, slightly more than half (52%) of Canadians report that either they or a family member have needed blood or blood products for surgery or medical treatment (CBS, 2012b).

Blood and blood components carry a potential risk of infectious disease transmission, such as HIV, hepatitis C, variant Creutzfeldt-Jakob disease (vCJD), and West Nile Virus, among others. Canada’s tainted blood tragedy resulted in approximately 1,000 blood recipients contracting HIV, with an additional 30,000 being infected with hepatitis C. Subsequently, the Krever Inquiry examined the safety of Canada’s blood supply and made numerous recommendations to improve the blood system (Krever, 1997). In response to the Krever Inquiry, Health Canada undertook significant changes to the blood regulatory system, which are described in detail later in this report. Health Canada representatives indicated that the current regulatory oversight has resulted in virtually no disease transmission through plasma products for the past 25 years.

Recent events have prompted renewed debate about the blood system in Canada. In particular, the application by a for-profit company, Canadian Plasma Resources, to Health Canada for a licence to collect plasma from paid donors raised concerns among stakeholders that providing payment for blood donations would introduce risk into the system by creating an incentive for low-income, high-risk groups to sell their plasma for cash. Concerns were also raised that allowing for-profit corporations into the blood system may result in commercial concerns taking precedence over the safety and well-being of Canadians. In stakeholder consultations in April 2013, Health Canada responded to these concerns by noting that plasma products available to Canadian patients have been manufactured for decades using plasma from paid donors; that since the introduction of modern manufacturing practices over 25 years ago, there have been no cases of transmission of Hepatitis B, Hepatitis C or HIV associated with a plasma product; that there are strict regulations in place for the screening and testing of donors, regardless of where plasma comes from and whether or not the donors were compensated; and that plasma collection centres must comply with very strict licensing regulations in order to operate (HPFB, 2013).

In addition, transplantation of tissues and organs also carries a potential risk of infectious disease transmission. Many diseases, including vCJD and West Nile Virus, can be transmitted through implanted tissues and organs (Greenwald, Kuehnert, & Fishman, 2012; WHO, 2010).

**Risks arising from shortages of biologic products**

Drug shortages in Canada have been an emerging issue for the last several years (Duffin, 2012; HESA, 2012; Labrie, 2012), affecting both human pharmaceuticals and biologics. There are many possible causes of drug shortages, including manufacturing quality problems, increased global demand, consolidation of production at a few sites, and economic reasons (Gray & Manasse, 2012). Manufacturing quality problems, for example, have been implicated in shortages of products produced by a limited number of suppliers, including influenza vaccine (Gray & Manasse, 2012). The global shortage of radioactive isotopes in 2009-2010, on the other hand, was caused by the shutdown of the National Research Universal reactor at Atomic Energy of Canada Limited’s Chalk River laboratories.
There is also a domestic shortage of tissues and organs for transplantation, due primarily to insufficient donations. It is well-recognized that there is an ongoing shortage of necessary tissues and organs in Canada (CBS, 2011; Peters, 2011; Shemie, Hornby, Chandler, Nickerson, & Burkell, 2011, p. 2085).

For patients and consumers, the potential consequences of domestic shortages of biologic products may include increased reliance on inappropriate alternatives and delayed medical procedures. Hundreds of Canadians die each year while waiting for organ transplants, including 285 patients in 2011 alone (CIHI, 2012), while the shortage of necessary tissues and organs creates reliance on suboptimal alternatives or requires them to be imported from other jurisdictions (CBS, 2011, p. 22). These shortages also increase motivation for desperate patients to engage in medical tourism (CBS, 2011, p. 160), which, aside from its ethical implications, carries its own risks. Of course, vaccine shortages put healthy people at greater risk for vaccine-preventable diseases.

Based on the preceding discussion of the risks associated with the use of biologics, as well as current industry trends and developments, continued government oversight of these products is necessary in order to help protect the health and safety of Canadians.

### 4.2 Alignment with federal priorities

The BP is aligned with federal priorities to improve the safety of health products through regulatory modernization.

The evaluation found the BP to be aligned with the priorities of the Government of Canada. The federal government has devoted substantial resources over the past decade to broader initiatives intended to improve the safety of health products in general through modernizing the regulatory framework for these products. The goal of renewal is to help ensure continued, timely access by Canadians to safe and effective health products in the face of several major challenges to the existing regulatory system. According to Health Canada, these challenges include an outdated regulatory toolkit; the system’s current incapacity to consider products through their entire lifecycle, from discovery through to examining “real-world” benefits and risks; the impact of scientific and technological changes, globalization of the marketplace, and a more informed and engaged public; and insufficient resources for long-term efficiency and sustainability (HPFB, 2007a).

---

14 For example, Prasad, Shukla, Huang, D’A Honey, & Zaltzman (2006) found that among 20 Canadian patients receiving kidney transplants outside the country, 52% experienced serious post-transplantation infections, including 14% with active tuberculosis and graft and patient survival was determined to be significantly worse than for patients receiving transplants in Canada.
The Branch’s plans for regulatory renewal were first articulated in the 2007 Blueprint for Renewal (HPFB, 2007a). The broad goals of regulatory renewal, as expressed in that document, include the following:

- taking a “product lifecycle” or “progressive licensing” approach to regulation, i.e., an approach to regulating health products that encompasses all stages of product development, and according to which products are assessed for quality, benefits, harms and uncertainties at pre- and post-market stages
- implementing regulatory interventions proportional to risk
- strengthening post-market surveillance, and compliance and enforcement
- learning from and collaborating with international counterparts
- enhancing transparency and openness
- basing regulation on scientific evidence
- ensuring the sustainability of the regulatory framework.

The federal government has undertaken several major initiatives that are clearly aligned with the objectives of regulatory renewal. A portion of the funding from these initiatives has been allocated to the Biologics program to conduct relevant activities. Beginning in 2003–2004, the federal government committed $190 million over five years under the Therapeutic Access Strategy (TAS) to “improve the timeliness of Health Canada’s regulatory processes with respect to human drugs” (Department of Finance, 2003). A major focus of the TAS was making pre-market regulatory decision making more efficient, timely, and transparent.

Beginning in 2006, the federal government allocated $172.5 million over a five-year period to the Therapeutic Product Safety Initiative (TPSI). The main focus of the TPSI was on post-market processes for the safety of therapeutic products. In addition, Health Canada was mandated to implement innovative regulatory frameworks for blood and for the safety of CTO.

More recently, Budget 2008 devoted $489.4 million under the Food and Consumer Safety Action Plan (FCSAP) to help ensure that consumer products and food are safe and beneficial to Canadians’ health (Health Canada, 2008b). The FCSAP is a horizontal initiative — involving Health Canada, the Public Health Agency of Canada (PHAC), the Canadian Food Inspection Agency (CFIA), and the Canadian Institutes of Health Research (CIHR) — with an overall goal to modernize food, health, and consumer product safety regulations and practices in Canada. FCSAP activities are expected to produce the long-term outcome of improved safety of health products on the market.

In 2008, the Government of Canada introduced comprehensive legislation (Bill C-51) embodying several elements of regulatory modernization, including the following:

- incorporating a progressive licensing framework where “the assessment of benefits and risks is to be based on scientific and objective evidence” and there is “ongoing assessment of information about a therapeutic product over its lifecycle”
- requiring prescribed classes of health care institutions to report adverse reactions
- introducing new administration and enforcement measures, including mandatory recalls of therapeutic products and federal power to recall the remaining stocks of a drug once it has been taken off the market due to safety concerns
• introducing a modernized framework for monetary fines and penalties by substantially increasing the fines for non-compliances
• expanding the powers of the Minister to compel holders of clinical trial authorizations, market authorizations, and establishment licences to compile information, conduct tests or studies, or monitor experience about the effects of therapeutic products on health or safety and report the information or results to the Minister (GoC, 2008a).

With the dissolution of Parliament on September 7, 2008, Bill C-51 did not become law. Since then, the federal government has taken a more incremental approach to regulatory modernization. Its most recent vision for modernization is expressed in the Regulatory Roadmap for Health Products and Food, released in May 2012 (Health Canada, 2012k). The Roadmap envisions a phased approach to modernization, with full implementation of all phases expected to be completed within a minimum of five years. Phase I initiatives with particular relevance to biologics include developing a stand-alone regulatory framework for blood and blood products (see Section 5.4.1), and creating a regulatory framework for the development, evaluation and approval of orphan drugs, which, as already noted, are drugs developed specifically for the treatment of rare diseases. BGTD representatives indicated that modernization of the regulatory framework for vaccines for human use is planned as part of Phase II, and updates to the semen regulations are also planned as part of regulatory modernization.

The federal government has signalled its commitment to regulatory modernization for health products by undertaking revisions to its existing cost recovery framework. The 2007 Cost Recovery Initiative (CRI) was in part a response to concerns raised by the Office of the Auditor General of Canada (OAG) in 2004 and 2006 about Health Canada’s ability to fulfill its regulatory requirements given its resource levels.15 The CRI was intended to contribute to a stable funding platform for regulatory services by increasing annual revenues for Health Canada from $47 million to $112.4 million, restoring the original cost-sharing ratio of 50%16 that occurred when cost recovery fees were first introduced in 1995 (Health Canada, 2010b). A major milestone of the 2007 CRI was achieved with the coming into force of Fees in Respect of Drugs and Medical Devices Regulations on April 1, 2011 (GoC, 2011a).

The major federal initiatives described above clearly demonstrate alignment of the BP with HPFB and federal priorities, particularly with respect to regulatory modernization for health products. Furthermore, BP activities are consistent with Health Canada’s current Program Activity Architecture (PAA) and, in particular, with the strategic outcome focused on helping to ensure that Canadians “are informed of and protected from health risks associated with food, products, substances and environments” and helping to ensure that products Canadians use “are as safe as possible, and that threats to health are addressed effectively” (Health Canada, 2012b).

---

15 More specifically, in 2006, the OAG recommended establishing baseline information for performance measurement, setting user fees based on clear and measurable service standards, and reviewing core funding to determine if it is sufficient (OAG, 2006).

16 A cost sharing ratio of 50% means that 50% of program costs are covered by user fees.
4.3 Consistency with federal roles and responsibilities

The BP is consistent with federal roles and responsibilities.

The BP is consistent with federal roles and responsibilities, some of which are defined in legislation. Health Canada’s mandate is set out in the Department of Health Act, which defines the Minister’s duties to include, among other things, the preservation of Canadians’ health and well-being, the protection of Canadians against risks to health and the spreading of diseases, investigation and research into public health, the establishment and control of safety standards and safety information on requirements for consumer products, and the collection, analysis, interpretation, publication and distribution of information relating to public health (GoC, 2006, sec. 4(2)). More broadly, the Minister’s jurisdiction covers all matters related to the health of Canadians that have not otherwise been assigned by the government to another body.

The Food and Drugs Act and the Food and Drug Regulations define the parameters of a drug and give legislative support to Health Canada’s role in regulating the use of biologics and taking actions to enforce compliance with those regulations. The Act limits the purposes for which any food or health product in general may be advertised or sold (GoC, 2008b, sec. 3). Sections 8–11 of the Act relate directly to drugs, prohibiting the sale of unsanitary or adulterated drugs, the use of inaccurate labelling, the misrepresentation of substances for other drugs, and the unsanitary manufacturing of drugs. The Regulations elaborate on the requirements for the safety and effectiveness of drugs designed, manufactured, or distributed in Canada, the standards for labelling and advertising, establishment licence requirements, GMPs, clinical trials, and adverse reaction/event reporting. The Regulations also specify the corrective actions that may be taken for drugs that are believed to not meet these requirements (GoC, 2012d).

With respect to biologics, Health Canada is responsible for regulating semen for assisted conception under the Assisted Human Reproduction Act (AHRA) and the Processing and Distribution of Semen for Assisted Conception Regulations (which were updated in 2000), and for regulating CTO for transplantation under the Safety of Human Cells, Tissues and Organs for Transplantation Regulations, which came into force in December 2007 (GoC, 2007). The CTO Regulations include provisions relating to CTO establishment registration, processing, packaging and labelling, storage and processing supplies, quarantine, errors and accidents, adverse reactions, investigations and reporting to Health Canada, record-keeping, personnel, facilities and equipment, and quality assurance systems.
5.0 Findings: governance and implementation

This section of the report presents the evaluation findings on program governance and implementation.

5.1 Program governance

Health Canada has made recent efforts to implement a governance structure for the Program. While some progress has been made in this area, challenges remain that may be addressed as new HPFB reporting structures mature.

The BP includes all activities undertaken by BGTD in relation to biologics, as well as relevant activities conducted by TPD, MHPD, the Inspectorate/RAPB, PPIAD, and RMOD.

In 2009, a Biologics Director Generals’ Coordinating Committee was created to “undertake a more horizontal integrated approach to the Biologics Program” and to “act as the pilot for program reporting for HPFB” (Health Canada, 2010c, p. 2).

In 2012–2013, HPFB implemented a new governance structure. Under the new structure, Pharmaceutical Drugs, Biologics, Medical Devices, Natural Health Products, Food Safety and Nutrition, and Nutrition Policy and Promotion are considered separate programs, each governed by a Program Executive Committee Sub-Committee. In addition, the Program Executive Committee is the most senior HPFB decision-making body for cross-program management and coordination. It consists of Director-General representation from each of the six program subcommittees. Within HPFB, a variety of committees and working groups also exist to manage various aspects of BP activity.

According to information provided by the Branch, in the previous governance structure, planning was done at the Directorate level and decisions were reported along program lines to senior officials. In the new model, it is intended that Programs will drive planning and reporting and Directorates will provide functional activities to deliver Program outcomes. The new approach is expected to more directly align the work done by all Directorates with the strategies, outcomes, and priorities of the Programs.

An October 2013 lessons learned report on the PEC found that the new governance approach had a number of strengths, including opportunities to provide a program (rather than directorate) overview, raise program challenges and issues, and improve coordination across the product lifecycle (RMD, 2013). However, some weaknesses and challenges were also identified, including a lack of focused/strategic discussions, frequent changes in direction, lack of follow-up on issues raised and actions decided, and lack of engagement from internal and external stakeholders.

17 Health Canada’s activities related to biologics have not historically been conceptualized as a “program.” This designation is relatively recent and appears to have occurred partly in response to the requirement for evaluation and the restructuring of Health Canada’s PAA in 2007–2008.
program partners, among others. The report concluded that while some progress has been made, the benefits of the approach “will most likely be realized in subsequent years when roles and functions have matured” (RMOD, 2013, p. 18).

5.2 Collaboration with external partners

BP partners collaborate with a variety of other federal government departments and agencies, as well as other external partners, to deliver regulatory activities related to biologics.

As part of the BP, the Inspectorate collaborates with the Canada Border Services Agency (CBSA) to ensure consistent administration of the Food and Drugs Act and Regulations through the Border Integrity Program, the objective of which is to strengthen Health Canada’s ability to make and support admissibility decisions at the border as they relate to health products.

As part of the BP, Health Canada collaborates with Canadian Blood Services (CBS) and Héma-Québec, as well as the provinces and territories, to operate the blood system in Canada. Through the Food and Drugs Act, the Food and Drug Regulations, and ongoing surveillance of the blood system, BGTD maintains oversight and approves any changes to the policies, practices, and procedures of the blood organizations (CBS, 2012a). CBS and Héma-Québec follow Health Canada regulations but are otherwise responsible for selecting operational locations, donor criteria, and procedures for blood collection, transportation, processing, quality control, and transfer to hospitals and clinics (CBS, 2012a; Héma-Québec, 2012).

BGTD also collaborates with PHAC in various surveillance activities related to transfusion of blood and blood products and transplantation of CTO, which are funded through the Blood Contribution Safety Program and the TPSI (PHAC, 2009). These surveillance programs include the following:

- the Transfusion Transmitted Injuries Surveillance System (TTISS) — a voluntary surveillance system involving collaboration between hospitals, provinces/territories, blood manufacturers, and PHAC to monitor adverse reactions associated with transfusions
- the Transfusion Errors Surveillance System (TESS) — which monitors errors associated with procedural and laboratory steps in the administration of blood products
- the Cells, Tissues and Organs Surveillance System (CTOSS) — which monitors transplantation adverse events related to CTO.

BGTD also collaborates with the Canadian Food Inspection Agency in the Bovine Spongiform Encephalopathy (BSE) Program, in place since 2003, by conducting research and risk assessment activities regarding human exposure to BSE and other Transmissible Spongiform Encephalopathies.

BGTD and MHPD also collaborate with PHAC and external stakeholders with respect to vaccines. BGTD is responsible for providing regulatory approval for new vaccines, while the National Advisory Committee on Immunization (NACI) makes recommendations around their use, supported by the Canadian Immunization Committee (CIC), which conducts further analysis.
On the basis of these recommendations and analyses, provinces and territories decide whether to publicly fund vaccines in their immunization programs. PHAC and MHPD collaborate in post-market surveillance of vaccines through the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS), the Immunization Monitoring Program ACTive system, and the Canada Vigilance Program.

BGTD engaged the Canadian Standards Association (CSA) to develop standards for CTO and blood (see Section 5.4.1).

Finally, BGTD collaborates with industry and other stakeholders through the Bilateral Meeting Program (BMP). Through this program, the directorate holds bilateral meetings with various national stakeholder organizations between one and four times per year. These meetings are held to discuss regulatory issues, exchange information, and share expertise and responsibilities. Finally, a variety of Expert Advisory Committees (EACs) and Expert Advisory Panels (EAPs) have played a role in guiding BP activities over the evaluation period.

5.3 Performance measurement

There are a number of performance measurement approaches developed to address various initiatives. Nonetheless, challenges remain related to performance measurement for surveillance and monitoring as well as compliance and monitoring activities.

There are a number of performance measurement strategies (PMS) that are directly relevant to the BP. These include frameworks for the TPSI, the FCSAP, and the CRI, as well as the HPFB logic model and accompanying PMS. Data on submission review performance, which include metrics on the volume of applications received, review times, workload, and backlog statistics has historically been the main focus of BP performance reporting. Detailed annual reports on submission review performance are used to inform senior managers and other decision-makers, and are also shared with industry. In addition, monthly dashboard reports were implemented with the CRI and are used to brief the Assistant Deputy Minister (ADM) and the Deputy Minister (DM). Health Canada also reports annually against established performance standards for the BP in the Departmental Performance Report (DPR), which is tabled in Parliament.

There remain, nonetheless challenges in performance measurement related to surveillance and monitoring as well as compliance and enforcement. These challenges are discussed in depth in the later sections of this report.

5.4 Program implementation

The BP has made progress over the period of the evaluation in implementing planned activities and, in the process, has responded to several emergent issues and challenges. The discussion below describes major regulatory developments pertinent to biologics, then provides an overview

---

18 It should be noted that according to BIOTECanada, “concerns have been expressed regarding potential overlap across the BGTD, NACI, and CIC mandates, including potential misallocation of scarce resources” (Cutcliffe, 2010, p. 16)).
of the drug regulatory process before going on to describe pre-market activities, post-market surveillance and monitoring, compliance and enforcement, and communications and stakeholder engagement activities under the period of the evaluation.\(^{19}\)

### 5.4.1 Regulatory development

**Health Canada has developed comprehensive regulatory frameworks to address the risks associated with cells, tissues and organs and blood and blood components, and work is ongoing to develop regulations for orphan drugs and to modernize the existing vaccine regulations.**

Beyond Bill C-51, which contained wide-ranging provisions applicable to biologics as well as human pharmaceutical drugs, two of HPFB’s most significant legislative and regulatory initiatives have focused on biologics — namely, the development of comprehensive regulatory frameworks for CTO and for blood and blood components. Regulatory development in these areas was undertaken to address the specific risks associated with these products. As noted, plans are in place to modernize the regulatory framework for vaccines.

**Cells, tissues, and organs (CTO)**

Recommendations for a regulatory approach to managing the risks associated with CTO date to the mid-1990s, when an external report on the safety of human organ and tissue transplantation in Canada recommended that national standards for organs and tissue transplantation be established; that a process be developed for the mandatory certification and accreditation of all transplant programs; and that these programs be accredited and inspected by a national agency (GoC, 2007). In response, Health Canada did the following:

- contracted the CSA to developed CTO standards, which were published in 2003 (GoC, 2007)
- issued a Directive and Guidance Document in 2003 to outline basic safety requirements for programs involved in processing of human CTO for transplantation
- undertook a National Review of establishments handling human CTO for transplantation, with the objective of assessing the adherence of Canadian establishments with the basic safety requirements set out in the Directive and the Guidance Document, in addition to taking appropriate actions to prohibit the distribution of unsafe products. Approximately 56 inspections were conducted during the National Review period (2003–2007)
- developed Phase I of the CTO regulatory framework — the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations) (GoC, 2007).

The CTO Regulations came into force in December 2007, except one section of the Regulations, which came into force in June 2008. The Regulations include provisions relating to CTO establishment registration, processing, packaging and labelling, storage and processing supplies, quarantine, errors and accidents, adverse reactions, investigations and reporting to Health Canada, record-keeping, personnel, facilities and equipment, and quality assurance systems. Health Canada is continuing to develop Phase II of the CTO regulatory framework, which will

---

\(^{19}\) To streamline the presentation of information, this organizational scheme does not align precisely with the program logic model. Nevertheless, all relevant program activities are covered.
include more comprehensive compliance monitoring and enforcement provisions, as well as surveillance and adverse reaction reporting strategies. The Phase II regulations will also extend to heart valves and dura mater (GoC, 2007).^{20}

BGTD representatives noted that due to scientific advancements in the field, product classification questions frequently arise in relation to CTO. Only minimally manipulated cells and tissues for non-homologous use are regulated under the CTO Regulations, whereas products that are more than minimally manipulated and/or for non-homologous use must undergo a pre-market authorization process under the *Food and Drug Regulations* (i.e., the latter are regulated as drugs, not as CTO). Product classification is done by the CTO Classification Committee, which is chaired by BGTD. Over the past seven years, since the coming into force of the CTO Regulations, the committee has classified approximately 100 products.

**Blood and blood components**

In October 2013, new *Blood Regulations* were published in Canada Gazette II and are expected to come into force in October 2014. Previously, all blood-related products — including whole blood, components, plasma and its derivatives, coagulation factor concentrates, and all other fractionated substances — fell under the broad definition of a drug in the *Food and Drugs Act* (GoC, 2008b, sec. 12; Krever, 1997, p. 118). Recommendations for regulations specific to the collection and processing of blood and blood components were made in 1997 by the Commission of Inquiry on the Blood System in Canada (the Krever Commission) (Krever, 1997, pp. 1067–1068). In response to the Krever recommendations, Health Canada immediately implemented a new establishment licence process, whereby all blood establishments would need to undergo routine inspections to assess compliance with the GMP requirements under the *Food and Drug Regulations* (BGTD, 2012b), and implemented a revised regulatory framework for plasmapheresis in 2006, which had remained unchanged for a 20-year period.^{21} Health Canada also contracted the CSA to develop blood standards, which were completed in 2004 and updated in 2010, and developed, between 2005 and 2012, a regulatory framework for blood and blood components, which was pre-published in Canada Gazette I in early 2012 (GoC, 2012a). The *Blood Regulations* include provisions relating to authorization and establishment licensing and registration, processing, labelling, storage, distribution and exceptional distribution, transformation, importation in urgent circumstances, quality management systems, errors and accidents, adverse donor or recipient reactions, and record-keeping.

**Vaccines**

Vaccination is widely considered among the most influential public health innovations in the developed world; in Canada, immunization has saved more lives over the last century than any other health intervention (CIHR, 2008, p. 7). Many vaccination programs are also highly cost-

---

^{20} Dura mater is the outermost of three membranes covering the brain and the spinal cord. It also lines the inner surface of the skull.

^{21} Plasmapheresis is a process by which blood is drawn from a donor and separated into plasma (the liquid portion of blood) and cellular portions (red and white blood cells) (GoC, 2002). The new regulations focused on updating regulations to reflect the practice of collecting source plasma via an automated (instead of a manual) plasmapheresis process and also clarifying the role of medical professionals in the plasmapheresis process; updating transmissible disease testing requirements and donor selection criteria and suitability; and clarifying requirements for serious adverse reaction reporting, recalls, and records management (GoC, 2005).
effective when compared to other types of public health interventions and, in many cases, are cost-saving. The market for vaccines in Canada, worth approximately $450 million annually (Cutcliffe, 2010, p. 6), has changed rapidly over the past decade. A resurgence in interest in vaccines has been driven by several factors, including: concerns about antimicrobial resistance; the absence of available vaccines for several existing and emerging infectious diseases; the perceived threat of bioterrorism; the discovery of new uses for existing vaccines; renewed interest in global health; and recognition of the need to maintain capacity to develop, manufacture, and test vaccines in Canada (CIHR, 2008, p. 9).

There are two broad classes of vaccines, namely preventive vaccines and therapeutic vaccines. Preventive vaccines aim to prevent infection by stimulating an immune response in healthy individuals,22 while therapeutic vaccines bolster immune response after a person has been infected by a pathogen or has even developed a disease (Moineon, Almond, & de Wilde, 2003, p. 462). Whereas preventive vaccines are well-established, therapeutic vaccines are an emerging technology.

In 2006, BGTD announced that it was undertaking a project aimed at modernizing the regulatory framework for vaccines for human use in Canada. One of the goals of the project was to address a number of outdated and highly specific regulations within Part C, Division 4 of the Food and Drug Regulations (BGTD, 2006). While Health Canada does not consider the out-dated regulations and the prescriptive nature of the vaccine-specific regulations to be a direct safety concern, their use “reduces the ability to respond to scientific and/or technical advancements and emergency situations” (Health Canada, 2007, p. 1).

A review on guidance for existing regulations within Division 4 of the Food and Drugs Act was conducted in 2008–2009. One of the goals of the review was to inform recommendations on a wide range of regulatory amendments that would revoke large sections of the outdated vaccine-specific regulations under Division 3 and 4 of the Food and Drug Regulations (Health Canada, 2010c, p. 16). To date, these plans have not yet resulted in regulatory amendments, though BGTD representatives indicated that this is planned as part of Phase II of HPFB’s regulatory modernization initiative.

Emerging/innovative biologic therapies

At present in Canada, other emerging/innovative biologic therapies such as stem cell therapy and gene therapy are treated as drugs under existing regulation. Health Canada recently issued a Notice of Compliance with Conditions (NOC/c) for Prochymal for use in paediatric patients (Clarke, 2012), making it the first country to approve a stem cell therapy. Developing its policy and regulatory approach to emerging/innovative therapies is likely to require Health Canada’s attention in future.


---

22 Because preventive vaccines are typically administered to healthy individuals, the costs of adverse health effects receive greater weight.
the regulation are the Committee for Advanced Therapies (CAT), a multi-disciplinary committee charged with providing the expertise necessary to review ATMPs in scientific areas relevant to advanced therapies, such as “medical devices, tissue engineering, gene therapy, cell therapy, biotechnology, surgery, pharmacovigilance, risk management, and ethics” (EC, 2007, chap. 7), as well as a framework for conducting long-term follow-up of safety and efficacy for patients and clinical trial participants treated with innovative therapies. The US FDA, for its part, appears to be taking a similar approach as Health Canada in treating emerging therapies as drugs under existing regulation. However, similar to the EU’s CAT, the FDA’s Centre for Biologics Evaluation and Research (CBER) has a multi-disciplinary Cellular, Tissue, and Gene Therapies Advisory Group that reviews and evaluates data relating to the safety, effectiveness, and appropriate use of advanced treatments. It is important to note that the committee approach is used by the FDA and the EU for all products, not just advanced therapies.

**Donor semen and assisted human reproduction**

As already noted, BGTD is responsible for regulating donor semen for assisted conception under the *Processing and Distribution of Semen for Assisted Conception Regulations*. The regulations are designed to address the risk of disease transmission through semen used in assisted conception by requiring that those who process or import semen notify Health Canada and observe safety-related requirements for screening, labelling, record-keeping, and tracing.

The semen regulations were last updated in 2000, and BGTD representatives noted that some aspects of the regulations are outdated. Plans to modernize the semen regulations were included as part of HPFB’s regulatory modernization initiative. According to BGTD, these updates are still a few years away.

BGTD representatives noted that since the *AHRA* became the responsibility of BGTD, there have been a number of challenges to putting regulations in place, including a constitutional challenge by the Province of Quebec and a criminal investigation by the RCMP.23 Policy discussions and the analysis of options are currently underway.

HPFB has undertaken many other regulatory and policy initiatives pertinent to specific stages of the product lifecycle, from clinical trials to market authorization to post-market surveillance, and, finally, to compliance and enforcement. These initiatives are described in the sections that follow.

### 5.4.2 The drug regulatory process

The current system of drug regulation in Canada focuses mostly on pre-market activities (TPD, 2010a). It is a “point-in-time” system, which is characterized by discrete regulatory interventions at specific, defined points, and in which drugs are evaluated for their risks and benefits primarily at the pre-market stage. Figure 1 illustrates the process, showing the order of the components and the areas where Health Canada has regulatory authority.

---

23 In a 2010 split decision, the Supreme Court of Canada declared some of the provisions of the Act unconstitutional. The RCMP investigation resulted in the laying of charges under the *Criminal Code* and the *AHRA*. After over a year in the courts, in December 2013, a plea bargain was struck and the accused pleaded guilty to the charges under the Act. BGTD representatives reported that this process consumed a considerable amount of time.
The regulatory process depicted above applies to all drugs, as defined in the *Food and Drugs Act*, including radiopharmaceuticals and biologic drugs, as defined in Schedule C and Schedule D, respectively, but does not apply to CTO or donor semen for assisted conception, which do not undergo clinical trials or pre-market review. Nonetheless, other aspects of the process — including post-market surveillance and compliance and enforcement of the applicable regulatory frameworks — do apply to these products.

Sections 5.4.3 through 5.4.7 describe the BP’s activities over the evaluation period in relation to the four main stages of the regulatory process — clinical trials, submission review and market authorization, post-market surveillance and monitoring, and compliance and enforcement. A description of the BP’s activities in the area of communication and stakeholder engagement follows.

### 5.4.3  Clinical trials

*Health Canada has taken numerous steps to strengthen the regulatory framework for clinical trials, but does not currently require sponsors to disclose the results of clinical trials.*

Clinical trial authorization is the first step in the licensing process and the first stage at which Health Canada has regulatory authority. To begin the process, sponsors submit a Clinical Trial Application (CTA) to Health Canada. CTAs are required for authorization to conduct clinical trials of new drugs in Canada, or marketed drugs where the proposed use is different from the approved use. A Clinical Trial Application Amendment (CTA-A) is an application that contains new information intended to update or modify a previous CTA approved by Health Canada.
After a sponsor submits a CTA or CTA-A, Health Canada begins the safety, efficacy, and quality review. Health Canada reviews the application for completeness and to determine if it is acceptable from a scientific and regulatory perspective, a process that is to be completed within 30 calendar days. If the Department identifies a deficiency, it will send, prior to the default date, a specific notice or letter to the sponsor, depending on the extent of the deficiency.

If Health Canada does not identify any deficiencies in the CTA or CTA-A, it will issue a No Objection Letter (NOL), and the sponsor will be free to conduct the clinical trial. Alternatively, if Health Canada fails to complete its review within the targeted 30-day period, the sponsor is allowed to proceed with the clinical trial. Health Canada has the authority to suspend and/or cancel the authorization to conduct a clinical trial, should it become aware of information that suggests the benefit/risk ratio of the clinical trial is not acceptable.

BGTD received 320 CTAs for biologics in 2012 and approved 298, which represents an increase of 24% in biologics CTAs received and an increase of 30% in approvals since 2004. By comparison, for pharmaceutical drugs, there was a 30% decline in the number of CTAs received and a 31% decrease in approvals over this same period. These trends are consistent with the industry shift, described in Section 4.1, toward development of biologics. See Appendix C for more detailed information.

**Strengthening the regulatory framework for clinical trials**

The current framework for clinical trials for drugs involving human subjects came into force on September 1, 2001. The regulations introduced a requirement that the clinical trial protocol be approved for each trial site by a research ethics board (REB) and that the clinical trial be conducted in accordance with GCPs, as well as requirements relating to record retention and adverse reaction reporting. An inspection program was introduced to verify that clinical trials comply with the new regulations.\(^\text{24}\)

Since these regulations were introduced, Health Canada has further strengthened the regulatory framework for clinical trials in the following ways:

- developing and updating guidance documents for sponsors, including, most recently, updated general guidance and guidance on the inclusion of women in clinical trials
- implementing risk-based approaches to monitoring and assessing clinical trial adverse reaction reports and selecting inspections of clinical trial sites, in response to the 2011 recommendations of the OAG, which although made specifically in the context of the pharmaceutical drugs program, are also applicable to the BP
- commissioning the Canadian General Standards Board to develop new voluntary standards for REBs, which were officially approved by the Standards Council of Canada in May 2013 and are now publically available for purchase through the Public Works and Government Services Canada website.

\(^{24}\) The clinical trial inspection program is described in detail in Section 5.4.7.
In addition, in July 2012, to address concerns that the requirement to file a CTA was posing an undue burden on researchers using positron-emitting radiopharmaceuticals (PERs) in basic clinical research, Health Canada implemented regulations defining which types of basic clinical research studies involving PERs fall outside the clinical trial regulations, and which ones require a CTA (GoC, 2012e).

A PER is a radioactive drug regulated by the BGTD and administered to patients undergoing a positron emission tomography (PET) scan. The radiation in the drug is detected by the scanner, which can then produce an image of a patient’s internal organs. The resulting images may be used to diagnose or determine the state of a disease, or may be used for non-diagnostic purposes, such as basic clinical research. Basic clinical research includes studies that are intended to advance scientific knowledge, but are not intended to fulfill any immediate diagnostic or therapeutic purpose, and therefore differ from clinical trials (GoC, 2012e). Because Part C, Division 5 of the *Food and Drug Regulations* did not distinguish between clinical trials and basic clinical research (GoC, 2001), researchers using PERs in basic clinical research were required to file a CTA. Health Canada determined that this requirement was posing an undue burden on these researchers (GoC, 2009).

Most recently, on May 29, 2013, Health Canada launched a new public database of drug clinical trials it had authorized. The database is mandatory for industry and contains specific information relating to Phase I, II, and III clinical trials in patients, including protocol number and title; drug name; medical condition; study population; date of NOL; sponsor name; study start and end dates; and trial status. The database includes trials that were authorized by Health Canada starting April 1, 2013 (Health Canada, 2013h).

By implementing the drug clinical trials database, Health Canada addressed its long-standing commitment to increase the transparency of clinical trial information. However, as Health Canada points out, the database is not a trial registry, and does not contain comprehensive information about each clinical trial (Health Canada, 2013h). In contrast, both the US and the EU have implemented mandatory registration of clinical trials, and have taken steps to require disclosure of clinical trial results.

In the US, registration of clinical trials has been a requirement since ClinicalTrials.gov was initiated as a result of the *Food and Drug Administration Modernization Act* of 1997, and a requirement for the submission of clinical trial results no later than 12 months after the completion of the clinical trial was introduced in 2007 with the *Food and Drug Administration Amendments Act* (NIH, 2012; US Government, 2007). Similarly, in the EU, since 2004, clinical trials must be registered with the EudraCT database. Since 2011, through the EU Clinical Trials Register, the public may access descriptive information on Phase II–IV adult clinical trials and

---

25 Health Canada promised to enhance public access to clinical trial information in the 2007 Blueprint for Renewal, and since then has encouraged sponsors to register their clinical trials of therapeutic products within 21 days of the trial’s onset with one of three publicly-accessible registries of the World Health Organization’s (WHO) Register Network. Both the OAG and the Senate Standing Committee on Social Affairs, Science and Technology (SSCSAST) have criticized the Department in recent years for not making more clinical trial information available to Canadians, despite its commitment to do so (OAG, 2011; SSCSAST, 2012).
paediatric clinical trials where the investigator sites are in the EU/European Economic Area (EMEA, 2012). Publication of results information is expected to be part of a revised Clinical Trial Directive, which is expected to be implemented in 2016.

Public disclosure of clinical trial results is important, given evidence from the literature that selective or biased reporting of clinical trial results — i.e., reporting only positive results and failing to report negative results — is quite common and can have serious consequences for patient safety. Further enhancing the amount of clinical trial information which is made publicly available, including information on the results of clinical trials, would be consistent with Health Canada’s commitment to enhancing transparency and openness as part of regulatory modernization, and would further align its approach with its main international counterparts.

Another area of regulatory divergence concerns paediatric clinical trials. Unlike Health Canada, both the US and the EU have the authority to require manufacturers to conduct paediatric trials. Health Canada representatives indicated that the Department does require paediatric trials before market approval if the manufacturer intends to obtain a paediatric indication; otherwise, approval will not be granted, and the Department has taken various steps to encourage sponsors to conduct paediatric studies.26 In the US, the Pediatric Research Equity Act of 2003 gave the FDA the authority to require manufacturers to conduct paediatric studies of new drugs that are likely to be used in a substantial number of children, or that are expected to provide meaningful benefits for children compared to existing treatments (IOM, 2008). Similar legislation was enacted in the EU in 2007, including a requirement that all applications for market authorization for new medicines include the results of all studies carried out as part of a mandatory Paediatric Investigation Plan, the aim of which is to ensure that the necessary data are generated “to determine the conditions in which a medicinal product may be authorized for the paediatric population” (MHRA, 2009).

The absence of similar regulations in Canada prompted the Senate Standing Committee to recommend in its 2012 report that Health Canada introduce regulations to require clinical trials to be designed to reflect the same population that can be “reasonably expected to consume the drug” once approved for sale in Canada and modify the drug approval process so that market approval is only granted if clinical trial evidence of the product’s safety and efficacy includes data on all population groups that can be reasonably expected to consume the drug (SSCSAST, 2012, p. 35).

In its response, Health Canada indicated agreement with the Committee’s recommendation that “drug development should include clinical trials in all patient populations that are reasonably expected to consume the drug,” and made note of several related initiatives that it had already undertaken (GoC, 2013c, p. 6). See below for a summary of these initiatives.

---

26 Health Canada has taken some steps to encourage sponsors to conduct paediatric studies. In 2006, regulatory incentives for paediatric studies came into force, providing a six-month data protection extension to sponsors submitting paediatric clinical trial information as part of an innovative drug submission (HPFB, 2007a, p. 27). Health Canada also recently released a discussion paper on the use of international paediatric information, which laid out three possible approaches to addressing Health Canada’s current lack of a regulatory mechanism or policy to encourage or require drug sponsors to submit new paediatric clinical trial data that are generated internationally (Health Canada, 2012).
Initiatives undertaken by Health Canada relating to inclusion of populations in clinical trial design

- publishing guidance on the inclusion of women in clinical trials, which includes recognition that clinical trials should be composed of subjects representative of the populations that the sponsor expects will use the product (Health Canada, 2012h)
- working with its international counterparts to exchange information related to pediatric drug development
- commissioning, in 2011, the Council of Canadian Academies to strike an independent panel to examine and report on “key science-based questions of public policy importance related to the development of therapeutic products for infants, children and youth”
- adopting ICH guidelines addressing the non-clinical and clinical requirements for drug development in women of child-bearing potential, pediatric, and geriatric populations
- implementing a six-month extension of data exclusivity for innovative drugs with pediatric data

Health Canada was of the view that amending the Food and Drug Regulations “to add requirements for clinical trial design and market authorization could result in unintentionally limiting access to new, innovative, and safe drugs” (GoC, 2013c, p. 7). Notwithstanding that both the EU and the US have the authority to mandate pediatric clinical trials, Health Canada noted in its response that mandating clinical trial design is “not consistent with international guidance related to drug development, or how comparable jurisdictions regulate drug development,” and suggested that changes in this area “would result in Canada being a less attractive jurisdiction for clinical trials” (GoC, 2013c, p. 7).

5.4.4 Submission review and market authorization

BGTD has met its performance targets for first review of biologics submissions since 2006. It is unknown how frequently OSEs and LRP evaluations identify issues that could affect the quality or safety of a product, and it is unclear if the BP collects this information in a systematic way.

Main types of drug submission relevant to biologics

- DIN application (Division 1)
- New Drug Submission (NDS) (Division 8)
- Priority NDS request
- Request for Notice of Compliance with conditions (NOC/c)
- Supplemental New Drug Submission (SNDS)
The second step in the licensing process is the regulatory submission. After the sponsor conducts the clinical trials, it may choose to seek market authorization for the drug by submitting an application to Health Canada. Health Canada’s role at the pre-market review stage is to evaluate the safety, quality, and efficacy of biologic drugs, ensuring that these products demonstrate clear benefits relative to their potential risks.

The pre-market approval process applies to all drugs, as defined in the Food and Drugs Act, including radiopharmaceuticals and biologic drugs, as defined in Schedule C and Schedule D, respectively. There is currently no pre-market approval process for biologic products meant for transplantation, which includes CTO. Instead, source establishments for CTO, establishments that distribute CTO to others within Canada, or establishments that import CTO for further distribution must register with Health Canada and conform to various safety standards. Similarly, there is no pre-market approval process for donor semen for assisted conception, although establishments that deal in donor semen are required to comply with specific regulations (see Section 5.4.7 for more information).

Submission types and process

There are several types of drug submissions. The DIN application process applies to “Division 1” drugs. A Division 1 drug is usually one that has been on the market for many years and whose safety and efficacy are well-established. Often, these drugs are available over the counter (OTC) (i.e., no prescription is required); however, it is important to note that no biologic drugs are OTC. Successful applications are issued a Drug Identification Number (DIN).

The New Drug Submission (NDS) process applies to “Division 8” drugs, which are new drugs, or those which have not been available for a long period of time. It also applies to Division 3 products (radiopharmaceuticals) and Division 4 products (biologics). An NDS is similar to a DIN submission, with some major differences, including much more rigorous regulatory requirements. The NDS process results in a Notice of Compliance (NOC), which authorizes the drug to be sold on the market, as well as the issuance of a DIN.

To begin the NDS process, a sponsor may submit a regular NDS (as described above), make a request for priority NDS status, or make a request for a Notice of Compliance with Conditions (NOC/c). A request for priority status may be made when there is substantial evidence to suggest the proposed drug will be useful against a debilitating or life-threatening disease or condition, or for which there is no other therapy marketed in Canada, or when the benefit/risk profile is an improvement over existing therapies marketed in Canada. The screening and review times are shorter for priority NDS than for regular NDS.

---

27 A DIN is an eight-digit numerical code that identifies a drug product’s brand name, manufacturer, ingredients, strength, pharmaceutical form, and route of administration. With the exception of radiopharmaceuticals, every drug product marketed in Canada (under the Food and Drugs Act and Regulations) has a DIN.
Just as for priority review status, an NOC/c may provide earlier access to “potentially life-saving drugs.” However, an NOC/c is different from a priority review in that it places a condition on the manufacturer to conduct further studies to confirm the benefits of the drug. These post-market surveillance studies are intended to monitor the safety and effectiveness of the product. 28

Submissions for subsequent entry biologics, or SEBs, are currently treated by Health Canada as NDS. Health Canada has explored the possibility of regulatory changes to accommodate SEBS and has developed a guidance document describing how SEBs are to be submitted (HPFB, 2010). BIOTECanada, the main industry association representing biologics manufacturers in Canada, has repeatedly shown its support for including SEBs in Health Canada’s regulatory modernization initiatives (BGTD, 2011a, 2011b, 2012a). Health Canada representatives indicated that the Department has determined that regulatory changes are not necessary at this time. They noted that experience will help to inform whether regulatory amendments were necessary, and pointed out that a similar approach was taken for generic pharmaceuticals. 29

Finally, since 2011, sponsors may submit an Extraordinary Use New Drug (EUND) submission, which provides a pathway for the authorization of new drugs under extraordinary circumstances by allowing sponsors to use results of animal studies in conjunction with results from limited data from human safety and efficacy studies to support their drug submission (Health Canada, 2013d). EUNDs are intended for extraordinary use in response to exposure to a chemical, biological, radiological, or nuclear substance where action is required to treat, mitigate, or prevent a life-threatening or other serious disease or disorder resulting from that exposure, or for preventative use in persons who are at risk of such exposure. The EUND regulations may apply in situations similar to the 2009 H1N1 pandemic, in which Health Canada had to rely on interim orders to approve H1N1 vaccines. 30

---

28 For pharmaceutical drugs, the sponsor may also submit an Abbreviated New Drug Submission (ANDS) when the proposed drug claims to be pharmaceutically-equivalent to an existing drug on the market. In this case, the submission must provide information that compares the performance of the “generic” product to the brand-name product. A Supplemental New Drug Submission (SNDS) or Supplemental Abbreviated New Drug Submission (SANDS) may be submitted when significant changes, such as changes to the dosage, manufacturing process, or labelling, are made to new drugs that have already been issued an NOC. However, ANDS and SANDS are not applicable to biologics.

29 Regulatory amendments were ultimately implemented introducing ANDS and SANDS for generic pharmaceutical submissions. In the case of SEBs, a comparison of the approval processes undertaken by Canada, the EU and the US for Omnitrope – to date, the only SEB approved in Canada – showed that despite some differences in legislation and submission requirements, all three regulators required roughly the same evidence to demonstrate comparability between the proposed product (Omnitrope) and reference product (Genotropin, in all three cases), and relied on the same core studies and reasoning methods (Courage & Parsons, 2011, pp. 218–220).

30 Under to the Food and Drugs Act, “The Minister may make an interim order that contains any provisions that may be contained in a regulation made under this Act if the Minister believes that immediate action is required to deal with a significant risk, direct or indirect, to health, safety or the environment (GoC, 2008b, sec. 30.1(1)). A 2010 lessons learned report on Health Canada and PHAC’s response to the H1N1 pandemic indicated that although the country’s experience with SARS helped lay the groundwork for improvements to Canada’s pandemic response capacity (PHAC & Health Canada, 2010, p. 93), the 2009 pandemic illustrated the continuing need for a permanent regulatory regime for the release and marketing authorization of pandemic influenza vaccines (PHAC & Health Canada, 2010, p. 75). At the time of the report, the EUND regulations were still under development; they did not become official regulation until 2011 (GoC, 2011b).
Review and market authorization

Once a drug is submitted, the screening processes and the safety, efficacy, and quality review processes take place. In comparison to Division 1 drugs, whose safety and efficacy are well-known, the review process for NDS involves a more in-depth clinical assessment of animal and human studies. The review process also usually includes an On-Site Evaluation (OSE) of the manufacturing facilities involved in producing the product; this is an element of the review process for biologics NDS that does not exist for pharmaceutical NDS. Because manufacturing of biologics typically involves more than one manufacturer, pre-approval OSEs are conducted for all of the manufacturing sites involved.

OSEs are routinely conducted for new product types and changes to biologics manufacturing processes and facilities, though they may be waived if BGTD has recently done an OSE for a similar product or if one has recently been carried out by a partner country in the Pharmaceutical Inspection Cooperation Scheme (PIC/S), a body of 44 international participating authorities that have come together to harmonize GMP inspection requirements and approaches across the world. OSEs are also conducted in the event of SNDS involving a change to chemistry or manufacturing.

BGTD representatives indicated that the purpose of the OSE is to confirm the information in the submission and make sure that there are no previously unforeseen factors that could result in a poor-quality product or increase the likelihood in the future of an error or accident that could lead to a contaminated product. The OSE is also used to verify that proper record-keeping processes are in place, which is critical to biologics, particularly those derived from human sources.

BGTD representatives noted that OSEs are one of the main factors contributing to a higher cost of submission review for biologics, compared to pharmaceuticals. Data provided by BGTD show that OSEs require, on average, 220 hours of staff time ($18,600 in salary), as well as an average of $8,502 in travel costs. Between 2000 and 2005, eight Notices of Deficiency were issued based on the outcome of OSEs (Health Canada, n.d). However, because the number of OSEs conducted in that time frame is not available, it is unknown how frequently OSEs identify issues that could affect the quality or safety of a product.

After successfully completing the screening process and the safety, efficacy, and quality review, the drug is issued a DIN, as well as an NOC. The NOC certifies that the drug is compliant with the Food and Drugs Act and Regulations, and authorizes it for sale on the market. Alternatively, the drug is issued an NOC/c, which grants market authorization of an acceptably-safe high-quality product, as long as manufacturers continue to comply with associated conditions (HPFB, 2011b). The goal of issuing an NOC/c is to provide access to a new or greatly improved treatment, prevention, or diagnosis of severe diseases or conditions for which there are no or inferior relevant drugs available, while continuing to monitor the risks presented by the drug and to evaluate its overall risk/benefit profile.

---

31  Calculated by BGTD based on NDS and SNDS received since September 19, 2012, with a final decision by March 20, 2014 (n=9).

32  As shown in Table 3, between 2004 and 2012 there were 129 NDS and 703 SNDS. An OSE was presumably conducted for all or most of the NDS as well as some of the SNDS (i.e., those involving a change to chemistry or manufacturing).
Post-market changes

After a product has received market authorization, sponsors are responsible for notifying Health Canada of any changes to the product. A different process is followed depending on the nature of the change and its likely or potential impact on safety, quality, and efficacy. Even if there are no changes to a drug, the sponsor must still submit annual notification of this to Health Canada (Health Canada, 2011b).

Lot Release Program

In addition to undergoing the pre-market process described above, biologic drugs (Schedule D) are subject to the requirements of the Lot Release Program (LRP), a risk-based program covering both pre- and post-market stages (GoC, 2012d, sec. C.04.015). Like the OSE, the LRP is a unique element of the BP; there is no analogous program for human pharmaceuticals. The LRP is discussed separately and in detail in Section 5.4.5, along with the BP’s regulatory research function, which like the LRP, has implications both pre- and post-market.

Special Access Program

Finally, under the Special Access Program (SAP), health care practitioners can gain access to drugs that have not yet received market authorization in Canada. The SAP is intended “for serious or life-threatening conditions where conventional therapies have failed, are unsuitable, or are unavailable either as marketed products or through enrollment in clinical trials” (HPFB, 2008). As part of regulatory renewal, Health Canada planned a review and modernization of the regulatory framework for the SAP, which was established in 1966. The review was expected to explore specific issues such as clarifying the circumstances under which authorizations may be issued or denied; providing for authorizations to be further reviewed where circumvention of clinical trial or NDS requirements are suspected; allowing for block releases of products in the event of public health emergencies; and establishing an ethical framework for permitting compassionate access to new therapies outside of clinical research (HPFB, 2007a). The status of this initiative is unknown.

In addition to the SAP, BGTD administers the Donor Semen Special Access Program “to provide access, in exceptional circumstances, to donor semen that would otherwise be prohibited from distribution under the Semen Regulations because it was not processed in accordance with all the regulatory requirements” (BGTD, 2011d).33 BGTD representatives indicated that the program is not being used as much as it once was.

---

33 Examples of exceptional circumstances include, among others, a woman or a couple who wishes to: (i) have another child using semen from the same donor they used for assisted conception in the past to ensure the children will be genetic siblings; (ii) use semen from a donor with specific physical characteristics; and, iii) use semen from a known donor.
Improving the submission review and market authorization process

Improving the quality and efficiency of the submission review and market authorization process for therapeutic products, including biologics, has been a priority for HPFB over the evaluation period. Facing increasing costs and substantial backlogs in the review process, HPFB has undertaken a variety of initiatives in order to reduce costs and improve efficiency and quality in submission review. These initiatives are briefly described below.

- **Service standards for cost-recovered activities.** To comply with the requirements of the *User Fees Act*, Health Canada implemented service standards for cost-recovered activities, including submission review (GoC, 2004, sec. 4.(1)). Service standards for submission review vary by submission type and class; for most NDS, the standard is 300 days (HPFB, 2011c).

- **New cost recovery framework.** In response to OAG concerns about HPFB’s ability to provide regulatory services given its existing resources, a new cost recovery framework for drugs and medical devices was implemented in April 2011 with the coming into force of the *Fees in Respect of Drugs and Medical Devices Regulations* (GoC, 2011a; HPFB, 2011a). At the same time, HPFB adjusted the way in which it determines whether it has met its performance standard for submission review. Prior to implementation of the new framework, HPFB aimed to complete 90% of all first decisions for each submission class within the target time frame. While HPFB still uses this metric internally, an additional metric was established with the implementation of the new cost recovery framework: requiring submissions, on average, to meet the target review time for first review for their submission class. In theory, processing submissions within established performance targets is expected to facilitate timely access to effective therapeutic products, thus increasing available treatment options without putting end users at greater risk.

- **Project management approach to submission review.** Under the TAS, Health Canada implemented a project management approach to submission review, which involved the creation of new “regulatory project officer” positions within BGTD to coordinate and guide each submission through the process, as well as the establishment of a Subcommittee on Submission Management and Good Review Practices consisting of senior managers within BGTD. The Subcommittee, which was first established in 2006, is a forum for senior management input, discussion, and oversight of biological and radiopharmaceutical submissions and related functions.

---

34 The *User Fees Act* provides that “if a regulating authority’s performance in a particular fiscal year in respect of a user fee does not meet the standards established by it for that fiscal year by a percentage greater than ten per cent, the user fee shall be reduced by a percentage equivalent to the unachieved performance, to a maximum of fifty per cent of the user fee” (GoC, 2004, sec. 5.1). The penalty (reduced user fees) is applied to submissions in the subsequent year when the average performance is more than 110% of the associated time target for the respective fee line(s).
• **Good Guidance Practices (GGPs) and Good Review Practices (GRPs).** BGTD has developed GGPs and GRPs for greater consistency in the development of guidance documents and submission reviews, respectively.

• **Electronic submission.** Health Canada has adopted the electronic Common Technical Document (eCTD) format established by the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use for E-Review. Despite slower-than-anticipated progress in implementing electronic submissions, Health Canada expanded the types of submissions in eCTD electronic-only filing format in 2011, and the number of electronic submissions has been increasing. More recently, under the RCC, Health Canada and the US FDA have been working toward the implementation of a Common Electronic Submission Gateway, using the current US gateway, that will allow “industry clients the ability to submit large electronic documents seamlessly to Health Canada and the US FDA” (GoC, n.d.). Through the Gateway, submissions will come to Health Canada through the FDA’s information technology infrastructure. A three-month pilot of the gateway project is underway.\(^{35}\)

• **Enhanced review capacity.** A Scientific Experts Database was launched in 2007 to assist in accessing external expert advice to work on drug and medical device submission reviews and participate on Scientific Advisory Panels and Committees. Health Canada reported that a total of 564 scientific experts are included in the database, who may be contracted to conduct aspects of submission review. According to Health Canada, external contracting costs have increased from approximately $350,000 in 2006–2007 to a forecasted $1.0 million in 2013–2014; according to BGTD, approximately 4% of the total was spent by BGTD.

• **Pre-submission meetings.** Although pre-submission meetings with sponsors were well-established by the early 1990s, both the Blueprint for Renewal and the FCSAP identified plans to improve this process. The main, though not the sole, purpose of the pre-submission meetings – which are optional at the discretion of sponsors – is to “provide scientific and regulatory advice to industry at early stages of product development” (HPFB, 2007a, pp. 22–23). In 2010–2011, guidance to industry on pre-submission meetings was made publically-available. Data provided by Health Canada show that between 2002 and November 23, 2012, BGTD held 721 pre-submission meetings, of which 45% were pre-CTA meetings and 33% were pre-NDS meetings (HPFB, 2012a).\(^{36}\) Industry key informants identified opportunities to improve the pre-submission meeting process by addressing long waits for meetings and ensuring that the principal reviewer is in attendance.

• **Use of foreign reviews.** In October 2011, as part of broader plans to improve review efficiency through increased use of foreign reviews, Health Canada launched the Use of Foreign Reviews Pilot Project, which was to run until March 2013. Products covered by the pilot include NDS, ANDS, SNDS, SANDS, NCs, and risk management plans (RMPs). According to a November 2013 evaluation of the pilot project, a total of 106 applications for biologics were submitted that were within the scope of the project; 18 submissions contained an unredacted foreign review supplied by the sponsor or obtained by Health Canada (Circum

\(^{35}\) The implications of this initiative for Health Canada’s current electronic submission infrastructure, which has been a work-in-progress for several years, are unknown.

\(^{36}\) The remainder were pre-DIN, pre-Notice of Compliance, and pre-SNDS meetings.
The evaluation noted that availability of foreign reviews was limited; few unredacted, complete foreign reviews were delivered with applications and few were received from foreign authorities following requests from Health Canada. Furthermore, BGTD reported that while sponsors may be willing to provide Health Canada with foreign reviews, it is not always possible for them to do so in time to be considered as part of the review. BGTD reviewers reported that the foreign reviews had a small positive impact on the review process, particularly with respect to improved risk identification and assessment. Overall, the evaluation noted that while the structure of the project was basically sound, some reviewers were resistant to using the analysis of others in forming their own conclusions. External key informants encouraged Health Canada to accept and use more information and approvals from foreign sources as a means of improving review efficiency.37

### The 2009 H1N1 pandemic

- In 2006, BGTD, the World Health Organization (WHO) and the Centre for Biologics Evaluation and Research (CBER) of the US FDA established an international Pandemic Preparedness Initiative. The Initiative, which brought together countries that have vaccine manufacturers within their borders, developed an international guideline on licensing a pandemic influenza vaccine. The guideline was based on a number of assumptions, including the assumption that an eventual pandemic would break in Southeast Asia, and would involve a bird flu strain.

- At the same time, BGTD created a pandemic influenza unit to handle review of eventual pandemic influenza vaccine submissions, and the company that had been contracted by PHAC to develop the vaccine began manufacturing based on the prototype – a bird flu strain.

- The influenza pandemic outbreak of 2009 occurred in Mexico not southeast Asia, and involved a swine flu, rather than a bird flu strain – thus proving wrong the assumptions that formed the basis for the international guideline.

These initiatives are expected to improve the efficiency and quality of the submission review process for biologics. The available data on submission review performance, which covers the period from the beginning of calendar year 2004 to the end of calendar 2012, are presented in Table 3.

---

37 The Use of Foreign Reviews project is one aspect of a larger Use of Foreign Regulatory Information (UFRI) project that also includes a Foreign Regulatory Scientific Committee, scientific advice, parallel reviews, joint reviews, and inter-regulatory discussion groups (HPFB, 2012b). A Foreign Regulatory Scientific Committee is in the pilot phase, and Health Canada also engages real-time scientific advice and discussions with other regulatory agencies (FDA, EMA) through Oncology, Paediatric, and Blood “clusters.”
Based on the percentage of review cycle completions within target, the timeliness of review fluctuated over the years for each submission type, and the 90% target was often not met. That said, in 2011 and 2012, 100% of review cycles for biologics NDS and SNDS were completed within the service standard. Health Canada data also show that, since 2006, BGTD has met its performance targets for first review.38 External key informants commented positively on the timeliness of the pre-market review process for biologics and the performance of BGTD in managing drug submissions.

The data also show that in 2006, BGTD successfully eliminated a substantial backlog in NDS and SNDS, and has maintained a backlog-free status in all years since then, with the exception of 2009. BGTD representatives explained that the backlog experienced in 2009 was due to the need to dedicate resources to the review of pandemic influenza vaccine submissions, in response to the outbreak of pandemic influenza in that year (see sidebar for more information). They estimated that between April 2009 and December 2009, between 20% and 30% of CVE resources were working on the pandemic influenza vaccine submission, and in addition to that, resources were brought in from other parts of the directorate. Responding to this public health emergency was, according to BGTD representatives, the busiest period the directorate had ever experienced. As shown in Table 3, the backlog was cleared in 2010.

A more detailed analysis of submission review data, taking into account factors such as changes in resource levels and number of applications over time, may provide further insight into Health Canada’s review performance. For example, it would be informative to consider annual review performance in light of the ratio of the number of full-time equivalents (FTEs) to the number of applications each year for each submission class. Similarly, it would be informative to consider the unit costs of completing reviews for each submission class (see Section 7.0 for a more detailed discussion).

Finally, in the context of submission review it is important to note that some external key informants expressed concern about the efficiency of Health Canada’s approach to regulating combination products. As an example relevant to biologics, it was observed that pathogen inactivation technology is regulated by the Medical Devices Bureau within TPD, while its application is regulated by BGTD. As a result, the manufacturer must submit two applications, rather than one which could be reviewed by both directorates. As another example, the regulation of kits containing several classes of product is perceived to be very onerous, particularly when the contents are not all produced by the same manufacturer. Combination products were discussed in detail in the evaluation of the Medical Devices Program, and the discussion is not repeated here.

38 For the purpose of this evaluation, the timeliness of submission review was assessed based on the percentage of review cycle completions within target. This indicator was selected in consultation with Health Canada, and includes all submission classes except Labelling only within these submission types, and all review cycles. This is not the only possible way to analyse review performance. Indeed, for the purpose of reporting on submission review performance in its departmental performance reports (DPRs) and under the Cost Recovery Initiative, Health Canada considers only Review 1.
Table 3: Submission review performance – biologics

<table>
<thead>
<tr>
<th>Submissions</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New Drug Submissions (NDS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of submissions received</td>
<td>14</td>
<td>12</td>
<td>13</td>
<td>17</td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Number in workload (at year end)</td>
<td>30</td>
<td>18</td>
<td>12</td>
<td>11</td>
<td>17</td>
<td>14</td>
<td>14</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Percentage in backlog</td>
<td>70%</td>
<td>55%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>21%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Number of review cycle completions</td>
<td>19</td>
<td>27</td>
<td>28</td>
<td>24</td>
<td>17</td>
<td>22</td>
<td>23</td>
<td>12</td>
<td>30</td>
</tr>
<tr>
<td>Percentage of review cycle completions within target</td>
<td>6%</td>
<td>8%</td>
<td>44%</td>
<td>100%</td>
<td>88%</td>
<td>82%</td>
<td>57%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Number of approvals</td>
<td>14</td>
<td>18</td>
<td>16</td>
<td>12</td>
<td>8</td>
<td>13</td>
<td>15</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Median approval time (calendar days)</td>
<td>959</td>
<td>1013</td>
<td>510</td>
<td>346</td>
<td>355</td>
<td>406</td>
<td>515</td>
<td>357</td>
<td>386</td>
</tr>
<tr>
<td><strong>Supplemental New Drug Submissions (SNDS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of submissions received</td>
<td>56</td>
<td>68</td>
<td>85</td>
<td>84</td>
<td>75</td>
<td>74</td>
<td>89</td>
<td>75</td>
<td>97</td>
</tr>
<tr>
<td>Number in workload (at year end)</td>
<td>73</td>
<td>43</td>
<td>38</td>
<td>38</td>
<td>40</td>
<td>54</td>
<td>52</td>
<td>41</td>
<td>55</td>
</tr>
<tr>
<td>Percentage in backlog</td>
<td>44%</td>
<td>49%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Number of review cycle completions</td>
<td>63</td>
<td>78</td>
<td>108</td>
<td>89</td>
<td>92</td>
<td>71</td>
<td>88</td>
<td>101</td>
<td>89</td>
</tr>
<tr>
<td>Percentage of review cycle completions within target</td>
<td>15%</td>
<td>22%</td>
<td>66%</td>
<td>98%</td>
<td>98%</td>
<td>94%</td>
<td>80%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Number of approvals</td>
<td>56</td>
<td>67</td>
<td>101</td>
<td>78</td>
<td>73</td>
<td>55</td>
<td>67</td>
<td>79</td>
<td>71</td>
</tr>
<tr>
<td>Median approval time (calendar days)</td>
<td>493</td>
<td>431</td>
<td>267</td>
<td>225</td>
<td>236</td>
<td>231</td>
<td>251</td>
<td>297</td>
<td>233</td>
</tr>
</tbody>
</table>

Sources: (BGTD, 2005, 2010b) and data provided by BGTD.

Definitions:
- **Submissions received** is the number of submissions received in a year using the filing date (the date the submission is considered administratively complete by Health Canada).
- **Workload** is the number of submissions in review status as measured at year end. These include both submissions undergoing first review as well as submissions where a subsequent review cycle was required to review company responses to issues raised by Health Canada.
- **Backlog** is workload that is over target.
- **Approvals** are Notices of Compliance (NOCs) issued or issuable. An NOC issuable is when a submission’s NOC is placed “on hold” awaiting authorization to market, due to Patent regulations or due to de-scheduling (from prescription to OTC).
- **Approval time** is the number of calendar days between the submission’s filing date and approval date, and includes any company time.
- **Review cycle completion** is counted upon the conclusion of an in-depth scientific review that results in a decision of approval or non-approval. It is considered to have occurred within target when the days taken to complete the review are within the performance standard.
5.4.5 Lot release program and regulatory research

Two important components of the BP, both of which distinguish it from the pharmaceutical drugs program, are the Lot Release Program and the BP’s regulatory research activities. These activities, and their role in the regulation of biologics, are described below.

Lot Release Program

As already noted, in addition to undergoing the pre-market process described above, biologic drugs (Schedule D) are subject to the requirements of the Lot Release Program (LRP), a risk-based program covering both pre- and post-market stages. Given that biologics involve the use of living organisms that are inherently more variable, difficult to consistently produce and characterize, and more sensitive to changes in starting materials and manufacturing than chemically synthesized drugs, the LRP is intended to provide additional monitoring of these products to help ensure their safety and efficacy (Health Canada, 2005a). Products subject to the LRP are assigned to one of four Evaluation Groups. Each group corresponds to a different level of regulatory oversight based on product risk levels. The criteria used to place products in the Evaluation Groups “include, but are not limited to, the nature of the product, the target population, the lot testing history in BGTD, and the manufacturer’s production and testing history” (Health Canada, 2005b). All products under review as a CTA or NDS, and sometimes a SNDS, are assigned to Group 1 during pre-market review, requiring that samples of consecutive lots of production be submitted for testing as part of the pre-market review process.

The LRP also involves a post-market component. At the post-market stage, biologics that have been issued an NOC are assigned to Evaluation Groups 2 to 4 before being sold in Canada. Manufacturers of biologic drugs in Groups 2, 3, and 4 are also required to submit Yearly Biologic Product Reports (YBPR). YBPRs contain information on drug substance and drug product lots, including test methods and results, reasons for any recalls and corrective actions taken, and other post-market information. This information is used to assess the ongoing safety and quality of the products, to verify the consistency of the manufacturing processes, and to highlight any trends; it may also be used to support assignment of the product to a different Lot Release Evaluation Group, or justify continuation of the current level of oversight (Health Canada, 2008d). See Table 4 for an overview of the LRP evaluation groups.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-approval stage</td>
<td>1a – Clinical Trial Materials</td>
<td>This group applies to clinical trial materials with authorized CTAs. Sponsors must complete a fax-back form and wait for signed response from BGTD before they may use the materials. In the case of Prophylactic Vaccines, samples must be submitted for testing by BGTD.</td>
</tr>
<tr>
<td></td>
<td>1b – Consistency Testing</td>
<td>This group applies to consistency samples associated with an NDS or SNDS. BGTD tests samples from 3 to 5 consecutively manufactured lots to ensure consistency of manufacturing.</td>
</tr>
<tr>
<td>Stage</td>
<td>Group</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------</td>
<td>--------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Post-approval stage</td>
<td>2 – Sample Testing and Protocol Review</td>
<td>This group includes products requiring the highest level of assessment after an NOC is issued. These products receive Targeted Testing, and each lot must receive a formal Release Letter from BGTD before they can be sold.</td>
</tr>
<tr>
<td></td>
<td>3 – Protocol Review and Periodic Testing</td>
<td>This group includes products requiring a moderate level of assessment after an NOC is issued. BGTD must provide a formal Release Letter for each lot before it is sold. BGTD reviews testing protocols but samples are not usually submitted for Targeted Testing. BGTD may request samples for Periodic Testing.</td>
</tr>
<tr>
<td></td>
<td>4 – Notification and Periodic Testing</td>
<td>This group includes products that do not receive BGTD sample testing or protocol review. The manufacturer of the drug must notify BGTD when each lot is sold in Canada. Release Letters are not required for sale, and BGTD may subject products to Periodic Testing.</td>
</tr>
</tbody>
</table>

Source: (Health Canada, 2005b)

Table 5 below shows the number of lots released each year under the LRP between 2009 and 2013. It is important to note that, as per the risk-based approach described above, not all of these lots underwent laboratory testing, but rather they were released on the basis of a satisfactory evaluation using the methodology applicable to their evaluation group.

**Table 5: Number of lots released, Lot Release Program, 2009–2013**

<table>
<thead>
<tr>
<th>Lots released under Lot Release Program</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1a: Clinical Trials</td>
<td>35</td>
<td>60</td>
<td>50</td>
<td>44</td>
<td>58</td>
</tr>
<tr>
<td>Group 1b: Consistency</td>
<td>92</td>
<td>92</td>
<td>111</td>
<td>88</td>
<td>72</td>
</tr>
<tr>
<td>Group 2: Sample Testing and Protocol Review</td>
<td>607</td>
<td>649</td>
<td>752</td>
<td>840</td>
<td>657</td>
</tr>
<tr>
<td>Group 3: Protocol Review and Periodic Testing</td>
<td>575</td>
<td>625</td>
<td>758</td>
<td>703</td>
<td>1,063</td>
</tr>
<tr>
<td>Group 4: Notification and Periodic Testing</td>
<td>1,262</td>
<td>1,388</td>
<td>1,263</td>
<td>1,882</td>
<td>1,444</td>
</tr>
<tr>
<td>International Release</td>
<td>0</td>
<td>205</td>
<td>5</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>International Non-pre-qualified Release</td>
<td>24</td>
<td>4</td>
<td>7</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>None (intermediates)</td>
<td>900</td>
<td>1,275</td>
<td>774</td>
<td>876</td>
<td>891</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3,518</td>
<td>4,343</td>
<td>3,720</td>
<td>4,465</td>
<td>4,198</td>
</tr>
</tbody>
</table>

Source: Data provided by BGTD.

While it is unknown how frequently the LRP identifies issues that could affect the quality or safety of a product, in a recent presentation, BGTD explained how the LRP allows the directorate to identify and address concerns at various stages of the regulatory process (Health Canada, 2013k).

- Testing prior to produce licensure can lead to the development of improved methods and better harmonization of quality control tests for new products globally.
- Identifying specific lots prior to lot release that are not compliant with market authorization, that are pending commitments, or that are incorrectly labelled can avoid on-market failure of the product or recall situations.
- Issues with product performance (such as adverse quality control trends observed by BGTD during lot release) can lead to discussions with manufacturers to resolve the problem (e.g., manufacturing or assay drift) before product failure.
BGTD representatives noted that the LRP is one of the main factors, along with OSEs, contributing to the higher cost of biologics reviews compared to pharmaceutical reviews. Data provided by BGTD indicate that there were 29.9 FTEs associated with the LRP in 2012–2013, representing salary costs of approximately $3.5 million. Quality sample testing requires, on average, 165 hours of staff time ($9,382 in salary).39

BGTD representatives observed that the workload associated with the LRP is increasing steadily, as new products are continuously being developed. They observed that the LRP’s risk-based approach helps to assure that LRP resources are used efficiently by giving more intensive oversight to higher risk products.

An example of the role of the LRP in the regulatory process for biologics is provided in the list below, using oversight of vaccines by way of illustration.

**Example of the importance of the LRP: oversight of vaccines**

- BGTD representatives indicated that oversight of vaccines through the LRP is important for two main reasons. First, because vaccines are given to healthy people (in many cases infants), this practice demands a high level of oversight. They observed that even products that have been licensed for decades continue to have problems in testing. Additionally, because vaccines often cover many diseases in one product, problems with one component can have implications for the entire production process, leading to vaccine shortages and the potential for outbreaks of vaccine-preventable diseases.

- Second, BGTD representatives indicated that there are two very large manufacturers of vaccines in Canada that export their products internationally. Thus, regulatory agencies around the world rely on BGTD’s strong oversight of these companies and their products.

- BGTD representatives noted that over the last two years, the LRP has allowed the directorate to risk-manage issues stemming from problems in the manufacture of the Bacille Calmette Guérin (BCG) and pertussis vaccines that are combined with many products.

**Regulatory research**

Regulatory research is another unique activity of the BP. Due to organizational changes within BGTD, three regulatory research divisions have recently been combined into a single division, housed within the new (since January 15, 2014) Centre for Biologics Evaluation (CBE). The Regulatory Research Division is responsible for conducting laboratory and experimental research designed to support the mandate of BGTD to regulate biologics. Research is conducted in the following areas: vaccines, stem cells, nuclear magnetic resonance spectroscopy of proteins, separation science, glycobiology, nanotechnology, and mass spectometry proteomics.

---

39 Calculated by BGTD based on NDS and SNDS received since September 19, 2012, with a final decision by March 20, 2014 (n=15).
Representatives of the Regulatory Research Division explained that the research performed is a combination of 1) forward-looking research to anticipate new issues in the regulation of biologics and 2) tactical method development and problem-solving. The former often informs policy development in emerging areas of regulation, whereas the latter supports the pre-market review, as well as the post-market functions of the BP through, for example, developing new methods to support the evaluation of biologics, or conducting laboratory analyses to support Inspectorate activities. Representatives of the Regulatory Research Division noted that work is ongoing to develop a governance framework that will allow the research function to be a readily available resource to all partner directorates in the BP while still performing the type of forward-looking research that can inform policy development. This effort is part of HPFB’s response to the recommendations of a 2013 audit of the management of scientific research within Health Canada (Health Canada, 2013a). The recommendations included implementing an enhanced branch-level governance structure for scientific research supported by the program governance; building on existing practices to define the spectrum of scientific research, detail scientific research plans, and monitor and report expenditures and personnel devoted to scientific research; and developing performance reporting for scientific research.

Representatives of the Regulatory Research Division also noted that the research function has encountered resource challenges. In 2012, the number of research scientists was reduced from eleven to eight as a result of a government-wide workforce reduction exercise. In addition to a proportionate reduction in the number of research projects, BGTD representatives noted that workforce reduction meant giving up specialized scientific expertise in certain areas. The research function has also had to work with smaller operating budgets as well as limited budgets for international conferences, which is the principal mode of training for research scientists.

5.4.6 Post-market surveillance and monitoring

Health Canada has taken numerous steps to improve post-market surveillance of biologics, while there are ongoing challenges with adverse reaction reporting and the use of adverse reaction report data. Health Canada lacks a standardized approach and centralized mechanism for systematically tracking its signal activities as well as its response to the recommended actions arising from completed signal assessments.

Following market authorization, Health Canada is responsible for undertaking post-market surveillance — also known as pharmacovigilance — to ensure that a product’s benefit/risk balance remains favourable. Health Canada defines pharmacovigilance as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem” (MHPD, 2009).

Whereas adverse reaction reporting has historically been the pillar of Health Canada’s (and other regulators’) approach to pharmacovigilance, especially for pharmaceuticals, MHPD representatives indicated that it is somewhat less important to the post-market surveillance of biologics. Because many biologic products are used to treat rare diseases that occur in small populations, these products have a limited number of exposures within the general population and therefore also generate a more limited number of adverse reaction reports. As a result, regulators must rely more extensively on other sources for post-market safety information, including international data, information provided by market authorization holders, and
individual case study reports. Furthermore, because of the small number of exposures and the fact that most adverse reactions to biologics occur over the longer term, longer term epidemiological studies are needed in order to obtain a more comprehensive understanding of a product’s safety profile.

Over the past decade, regulators have increasingly recognized the need to enhance post-market surveillance in order to better protect patient health and safety. As part of its broader regulatory modernization initiative and its intended shift toward a product lifecycle approach to regulation, Health Canada has taken a number of steps to strengthen its approach to post-market surveillance and monitoring. These initiatives, along with outstanding challenges and issues, are discussed below, with particular attention to those with most relevance to biologics.

Enhancing adverse reaction reporting and analysis

Under the Food and Drug Regulations, “serious adverse drug reaction reporting” is mandatory for manufacturers. In addition, health professionals, institutions, and members of the public may submit adverse reaction reports on a voluntary basis. The CTO Regulations also contain mandatory adverse reporting requirements for source establishments. The text below provides more detailed information on adverse reaction reporting requirements.

Adverse reaction reporting in Canada for biologics

• **Manufacturers:** Under the Food and Drug Regulations, “serious adverse drug reaction reporting” is mandatory for manufacturers. Manufacturers must submit all information relating to the incident within 15 days of receiving or otherwise becoming aware of a serious adverse reaction, whether it occurs inside or outside of Canada. Completed reports may be mailed or faxed to Health Canada. Since 2011, manufacturers are also required to prepare annual summary reports on all adverse reactions within the previous year and the manufacturer’s analyses of those incidents, and submit these reports to the Minister of Health upon request.

• **Health professionals, institutions, and members of the public:** Adverse reaction reporting is voluntary for these stakeholders. Standardized reports are available for consumers and health professionals, and may be mailed, faxed, or completed online. Reporting may also be completed by telephone.

• **Adverse reaction reporting for CTO:** Under the CTO Regulations, source establishments conducting an investigation of an “unexpected serious adverse reaction that is thought to involve the transmission of an infectious disease or disease agent” must provide the Minister with reports providing information related to the adverse reaction. Source establishments must file a preliminary report within 24 hours after the start of the investigation, and updates within 15 days after the start of the investigation and then every 15 days after that until the final report is made.

• In addition, the CTO Regulations also require establishments that are not source establishments (i.e., transplant establishments) to notify source establishments and importers if they have reasonable grounds to believe that an error or accident or an unexpected adverse reaction has occurred.
All adverse reaction reports are submitted to the Canada Vigilance Program, which was established in 2007 as the new name for the Canadian Adverse Drug Reaction Monitoring Program. Since then, adverse reaction reporting has increased dramatically.

Figure 2 shows the growth in the number of domestic adverse reaction reports relating to biologics received by Health Canada between 1999 and 2012; pharmaceuticals are included by way of comparison. In total, 70,112 adverse reaction reports have been received for biologics. The annual number of reports relating to biologics grew 4,258% over this period, from 500 reports in 1999 to 21,792 reports in 2012. Most of this increase has occurred since 2007. The adverse reaction report data pertaining to biologics encompasses a number of different types of products, including biotechnology products; blood components; CTO; radiopharmaceuticals; and vaccines and diagnostics. The vast majority of biologics reports (82%) relate to biotechnology products.

Domestic adverse reaction reports are only a fraction of the total number of adverse reaction reports received by Health Canada, since foreign reports, which represent more than 90% of all reports received, are not entered into the Canada Vigilance Database. To enhance adverse reaction reporting and analysis, including analysis of foreign adverse reaction reports, Health Canada implemented electronic reporting of adverse reactions for industry in April 2013, and aims to receive more than 80% of all MAH adverse reaction reports electronically by December 2014. Health Canada had already implemented an electronic reporting system for health professionals in 2013, allowing them to submit adverse reaction reports directly via the MedEffect website.

Figure 2: Domestic adverse reaction reports received, biologics and pharmaceuticals

Source: Data provided by Health Canada

40 These data were extracted by Health Canada from the Canada Vigilance Database.
In addition to introducing electronic reporting, Health Canada has also addressed the long-standing problem of under-reporting of adverse reactions by health care professionals in several ways (see Table 6 for external key informants’ perspectives on barriers to adverse reaction reporting, as well as their suggestions for improvement). Initiatives in this area include producing a guidance document to assist health professionals in reporting adverse events (MHPD, 2011a); providing education activities to health professionals through employees working in the regions; and engaging Accreditation Canada, the body responsible for accrediting Canadian hospitals and other health care institutions, to establish national adverse reporting standards within the existing accreditation system, which were released in January 2013.

### Table 6: External key informant views on adverse reaction reporting

<table>
<thead>
<tr>
<th>Perceived barriers</th>
<th>Suggested solutions</th>
</tr>
</thead>
</table>
| - Lack of clarity regarding reporting requirements, for example:  
  - who is responsible for reporting, especially if a patient is being seen by multiple clinicians  
  - whether the reaction should be reported if it was expected, or if it is attributable in whole or in part to inappropriate use of a product  
  - how serious the event must be to merit reporting  
  - how or if to report adverse events associated with low-risk products  
- Time constraints  
- A reporting process that is not perceived as user-friendly  
- Concern about potential negative consequences  
- Lack of feedback from Health Canada regarding how and whether the information they provide will be used | - Expanding marketing efforts  
- Engaging professional and industry associations to encourage their members to report  
- Streamlining the reporting process  
- Providing feedback to those who report  
- Examining approaches employed in other jurisdictions  
- Reimbursing practitioners for reporting and implementing mandatory reporting |

Most recently, on December 6, 2013, Bill C-17, the Protecting Canadians from Unsafe Drugs Act (Vanessa’s Law) was announced and is currently in second reading (GoC, 2013a). This legislation proposes changes to the Food and Drugs Act that are expected to improve Health Canada’s ability to collect post-market safety information, including a proposed amendment introducing mandatory reporting of adverse reactions by health care institutions.41

Despite progress in these areas, there remain some challenges related to adverse reaction reporting, particularly for CTO, blood and blood components, and vaccines. With respect to CTO, focus group participants representing CTO establishments expressed concerns about a lack of clarity surrounding the mandatory adverse reaction, error, and accident reporting requirements and risk mitigation measures for CTO source establishments. For example, when an adverse reaction is observed but establishments are unsure of the cause, it is unclear whether it is necessary to report and/or notify other stakeholders within 24 hours; similarly, when quarantine is required, it is unclear whether or not it applies to all tissues from the same donor. Focus group participants also expressed concerns about the process of reporting adverse reactions. In particular, the requirement to notify Health Canada of an adverse reaction, suspected error, or accident within 24 hours is seen as excessive for certain circumstances. Participants were of the view that these regulatory requirements do not fully consider the ramifications of informing.

---

41 Health Canada initially announced its intention to introduce mandatory serious adverse reaction reporting for health care institutions as part of the FCSAP, and a provision for mandatory reporting by health care institutions was included in Bill C-51 in 2008, which did not become law.
stakeholders of an issue that may ultimately prove to be non-existent. There is also a perceived need for clearer definitions of “adverse reaction,” “error,” and “accident,” as well as clearer guidelines for reporting, depending on the specific type of CTO involved. Health Canada has published a guidance document for CTO establishments that outlines regulatory requirements, including the requirements relating to adverse reaction, error and accident reporting, as well as a brochure on error and accident reporting.

Focus group participants generally agreed that Health Canada does not do enough follow-up with organizations after they submit an error, accident, or adverse reaction report. Rather than receiving a form letter thanking them for their report, participants said they would appreciate receiving suggestions from Health Canada regarding ways of preventing similar incidents from occurring in the future. Other suggestions for Health Canada included distributing summary reports of adverse reactions on an annual basis to give CTO establishments an idea of what other establishments are reporting and what they can do to prevent similar problems in their own organization, and including case studies as appendices to guidance documents to illustrate appropriate risk mitigation steps after an adverse reaction. Participants emphasized that as the entity charged with improving the safety of CTO in Canada, an important aspect of Health Canada’s role should be to encourage collaboration and sharing of information with and among CTO establishments concerning best practices, in order to improve compliance with regulatory requirements.

With respect to blood, external key informants noted that there may be a need to clarify adverse reaction reporting requirements to the TTISS and to Health Canada, respectively. As noted earlier in this report, TTISS is a voluntary surveillance system involving collaboration between hospitals, provinces/territories, blood manufacturers, and PHAC to monitor adverse reactions associated with transfusions.

In a related vein, MHPD representatives suggested that there may be significant under-reporting to the Canada Vigilance Program of adverse reactions related to blood, CTO, and vaccines. This may be, in part, because PHAC and/or the provinces and territories also have responsibilities for post-market surveillance of these products through the TTISS, the CTOSS, and the CAEFISS. Although MHPD and PHAC work together regularly to reconcile the information on adverse reaction reports for these products in their respective databases, MHPD does not have the ability, due to confidentiality provisions, to directly access PHAC and provincial/territorial databases. As a result, MHPD does not have access to comprehensive adverse reaction report data for these products, which limits the usefulness of these data for the purpose of post-market surveillance. In 2010, the Lessons Learned Review on the PHAC/Health Canada response to the 2009 H1N1 pandemic recommended that the parties involved (PHAC, Health Canada, and the provinces and territories) finalize agreements on sharing vaccine surveillance information across jurisdictions and implement an integrated surveillance system for immunization, including monitoring adverse events (PHAC & Health Canada, 2010).
MHPD representatives indicated that the directorate is planning to create a CTO surveillance network with some of the main graft centres in Canada. This initiative is intended to address the fact that some adverse reactions from organ graft centres were not being reported to the source establishments, which are responsible for reporting these adverse reactions to Health Canada. By connecting major organ graft centres with source establishments and Health Canada, the network is expected to facilitate reporting of adverse events to Health Canada, as well as facilitate open communication among the graft centres and Health Canada on the usefulness of these reports.

**Enhancing signal detection and assessment**

In addition to enhancing adverse reaction reporting and analysis, Health Canada has also sought in recent years to enhance the detection and assessment of safety signals by broadening the sources of information it monitors for potential signals and developing Standard Operating Procedures (SOPs) to guide the process. Health Canada defines a safety signal as a “new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory [sic] action” (MHPD, 2012d).

Sources monitored for potential safety signals include the scientific literature, media communications, public communications from other regulatory agencies, safety information from MAHs (such as adverse reaction reports and periodic safety update reports), information from Health Canada’s pre-market bureaus, and adverse reaction information voluntarily submitted to the Canada Vigilance Program or other adverse reaction databases (MHPD, 2013).

Health Canada has begun developing and implementing strategies such as targeted surveillance and data mining to systematically monitor adverse reaction reports for potential safety signals. MHPD representatives indicated that data mining is likely to have limited usefulness for post-market surveillance of biologics, since many biologic products are used in small populations and therefore will not generate a sufficient number of adverse reaction reports in the Canada Vigilance Database to support data mining. However, MHPD does carry out targeted surveillance using Canada Vigilance data for targeted adverse events in relation to specific, targeted drugs.

MHPD representatives noted that while post-market surveillance of pharmaceuticals relies extensively on analysis of adverse reaction reports to identify safety signals, post-market surveillance of biologics relies more heavily on PSURs and international data from literature scanning and interactions with other regulatory agencies. For example, MHPD participates in a quarterly teleconference with the FDA, the TGA, and the EMA to compare safety signals, and has a medical officer embedded in the EMA who participates in its pharmacovigilance risk committee. MHPD representatives also noted that individual case histories are an important source of safety signals for biologics, since there are few follow-up studies of these products being conducted by manufacturers given the small number of patients exposed. MHDP reported that most of the signals detected for CTO and blood come from individual case study reports.

MHPD also has longitudinal registries for following up with patients on specific drugs or diseases.
Within MHPD, two bureaus are responsible for monitoring sources for potential signals relating to biologics, as summarized in Table 7. The Marketed Health Products Safety and Effectiveness Information Bureau (MHPSEIB) monitors adverse reaction reports for potential safety signals, while the Marketed Biological and Biotechnology Signal Identification and Coordination Working Group (MBB SIC WG) within the Marketed Biologicals, Biotechnology and Natural Health Products Bureau (MBBNHPB) is responsible for monitoring all other information sources for potential safety signals relating to biologics.

<table>
<thead>
<tr>
<th>Bureau</th>
<th>Responsibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marketed Health Products Safety and Effectiveness Information Bureau (MHPSEIB)</td>
<td>Monitors spontaneous adverse reaction reports submitted to the Canada Vigilance Program using case review and case series analysis, targeted surveillance, and data-mining.</td>
</tr>
<tr>
<td>Marketed Biologicals, Biotechnology and Natural Health Products Bureau (MBBNHPB)</td>
<td>Within this bureau, the MBB Signal Identification and Coordination Working Group (MBB SIC WG) is responsible for detecting potential signals relating to biologic products by monitoring all other information sources.</td>
</tr>
</tbody>
</table>

MHPD has developed a standardized process for detecting and assessing safety signals, regardless of the type of product involved. After a potential signal is detected and given a preliminary assessment, it is presented to and discussed by the signal prioritization committee. The committee is responsible for classifying potential signals in one of three ways:

- an identified signal, if information suggests a link exists between product and event, and risk management is possible
- a potential product issue awaiting further information, if there is insufficient information to support the link now, but information could become available within 18 months and allow for risk management
- a dismissed signal, if information to support the link between product and event is not currently available, is unlikely to become available soon, or if risk management is impossible regardless of the investigation findings (MHPD, 2012d).

Identified signals are assigned for signal assessment, during which evaluators conduct a comprehensive critical appraisal of the evidence available, analyse possible risk management options, and make recommendations for action (MHPD, 2012e). Potential recommendations may include standard or enhanced monitoring; requesting additional information from the MAH; requesting the MAH to undertake a benefit-risk assessment, develop a pharmacovigilance plan, or develop a risk management plan; recommending changes to the product labelling; recommending issuance of a risk communication; requesting consideration by the Drug Safety and Effectiveness Network (DSEN); and recommending a full issue analysis to determine if the product should be withdrawn from the Canadian market.

A large number of SOPs have been developed over the last few years to support the signal detection, prioritization, and assessment process, while others are still in development.
Based on analysis of administrative data provided by Health Canada, the following observations can be made about MHPD’s signal detection and assessment activities:

- Of 6,505 detected signals relating to biologics between 2008 and 2012, approximately 97% were dismissed before undergoing a preliminary review, and less than 1% were prioritized for signal assessment. The most common reasons for dismissing biologics signals at first screening were recorded as being: confounded by indication (46%); no safety issue demonstrated (22%); and product not marketed in Canada (10%).

- A total of 113 signal assessments for biologics were completed between 2005 and 2012. The most commonly-recorded sources of safety signals were the MAH (38%) and the MBB SIC WG (18%). Note, however, that the MBB SIC WG is tasked with detecting potential safety signals from all possible sources and is itself not a “source” of safety signals. This speaks to the need for greater clarity in recording information.

- The most common recommendations resulting from completed biologics signal assessments were standard monitoring (28%); requesting additional safety information (26%); and changes to the product labelling (21%).

MHPD representatives explained that, compared to pharmaceuticals, MHPD uses a lower threshold for identifying issues as potential signals in the case of biologics. They also noted that most of the adverse reactions related to biologics are serious in nature, but because of insufficient exposure data, biologics signals more often become subject to ongoing monitoring. Please see Appendix C for more detailed information.

The above analysis was complicated by a variety of limitations in the data. For example, signal detection and assessment activities are tracked through a series of Excel spreadsheets maintained by various groups within MHPD, rather than through an integrated or centralized database accessible to all parties involved. There is no way to easily link or match records contained within these spreadsheets; unique identifiers are assigned to signal assessments, but not to signal detection activities, and, as a result, matching signal detection with assessment records must be done manually. In addition, there are many inconsistencies in the ways in which data are recorded, as well as missing data, with implications for data reliability and validity. There is also widespread use of open-ended, text-based fields for data entry, necessitating time-consuming coding to enable quantification or analysis.

In addition, there has historically been no centralized mechanism or tool in place for systematically tracking Health Canada’s response to the recommended actions arising from completed signal assessments. In 2011, as part of its audit of the pharmaceuticals program, the OAG recommended that such a system be implemented. While a tracking tool for safety recommendations for pharmaceuticals has recently been introduced (Health Canada, 2013o), it is specific to TPD and is limited to actions that fall within its area of responsibility (i.e., changes to product labelling). A similar system has not yet been implemented to track Health Canada’s response to recommended actions that fall within the purview of other directorates, or its response to recommendations for biologics signals. According to program representatives, a system to monitor outcomes of biologics signals will be considered for future implementation.
Implementing risk management and pharmacovigilance planning

Risk management planning involves detailing the potential risks posed by a health product and steps to be taken to reduce the potential for harm (Health Canada, 2009b), while pharmacovigilance planning refers to the pre-authorization development of a monitoring process to collect safety information on an ongoing basis after a drug has reached the market. Under the FCSAP, Health Canada intended to implement a more structured, comprehensive and systematic approach to pharmacovigilance planning, and, as a complement to pharmacovigilance plans (PVPs), create a new program requesting industry to submit RMPs on a voluntary basis. Health Canada intended eventually to propose legislative and regulatory amendments to compel manufacturers to submit RMPs and PVPs routinely as part of the pre-market process.

Requirements for RMPs in Canada

**Mandatory components:**

- the Safety Specification that summarizes all important safety information concerning the product, including gaps in knowledge
- the Pharmacovigilance Plan that includes known and potential safety concerns and the methods by which the manufacturer will monitor new safety information
- a Risk Minimization Plan that proposes methods for minimizing known and potential safety risks

**RMP submission:**

- as a component of a product licence submission
- on request by Health Canada in any case where the department deems it relevant to risk/benefit decisions, such as a new active substance, a change in indication, or the introduction of a product to a class with a previously-existing safety risk

Since these plans were announced, pharmacovigilance planning has been subsumed within the broader concept of risk management planning. In 2009, Health Canada adopted ICH E2E on pharmacovigilance planning and established interim requirements for RMPs based on the guidelines of the European Medicines Agency (EMA).

Program representatives indicated that BGTD currently requests RMPs to be submitted as part of all biologics NDS, and as part of SNDS that have clinical-related data. MHPD reviews all RMPs submitted with a pre-market application and any RMPs submitted in subsequent post-market submissions. Between 2009 and 2013, MHPD received a total of 187 RMPs, and completed (i.e., reviewed) 193 RMPs. See Appendix C for additional information.

Health Canada currently does not have the authority to compel submission of RMPs. While sections proposed under Bill C-17 may grant broad authority to Health Canada to impose terms and conditions on market authorizations, it is unclear if Health Canada has specific plans to pursue the authority to compel RMPs in future. In contrast, both the EMA and the FDA have legal authority to compel submission and levy fines for noncompliance (MHPD, 2009).
FDA has had the authority since 2007 to require sponsors to submit a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of a drug outweigh the risks (US Government, 2007), and may do so for new drugs and drugs already on the market, depending on specific criteria. In the EU, since new pharmacovigilance legislation was implemented in July 2012, RMPs are mandatory for all applications for a new marketing authorization; they are also usually required when there is a significant change in authorization, such as a new dosage, route of administration, or indication. RMPs can also be requested by the regulator whenever there is a concern about a risk affecting the benefit-risk balance of the medicine, or be submitted on the initiative of the manufacturer for newly-identified safety issues. The EU legislation also requires a summary of the RMP to be made public (EMEA, 2013a; MHPD, 2009).

**Enhancing post-market safety reporting by manufacturers**

The Periodic Safety Update Report (PSUR) is an internationally-standardized report by a manufacturer to regulatory authorities on the worldwide safety of a marketed drug product (MHPD, 2012c). In Canada, PSURs are expected to cover information in six-month intervals. They may be submitted voluntarily by manufacturers, or Health Canada may request a PSUR from the manufacturer following the identification of a safety issue (MHPD, 2012c). The submission of PSURs may also be required as the result of an NOC/c or other commitment following market authorization, or be negotiated during the authorization process. Otherwise, PSURs are not mandatory under current regulations.

Between calendar years 2009 and 2013, MHPD received 729 PSURs (both solicited and unsolicited), and completed (i.e., reviewed) 726 PSURs (both solicited and unsolicited). In addition, between fiscal years 2009–2010 and 2013–2014, BGTD accepted a total of 44 PSUR-Cs (PSUR-Confirmatory). See Appendix C for more information.

Under the FCSAP, Health Canada planned to enhance its existing program for collecting and reviewing PSURs and advance amendments to the *Food and Drugs Act* to give it the legislative authority to compel manufacturers to submit PSURs. Health Canada has introduced two levels of PSUR review and has set performance standards for the review of PSURs. Most recently, it announced that it was moving toward implementing ICH E2C(R2) guidance and Periodic Benefit Risk Evaluation Report (PBRER) reporting “in order to align with international best practices and reduce the burden on industry by allowing them to submit either [a PSUR or a PBRER] to satisfy the applicable regulatory requirements in Canada” (Health Canada, 2013l).

The “applicable regulatory requirement” in question is C.01.018 of the *Food and Drug Regulations*, which since 2011 has required MAHs to analyze adverse drug reaction data and prepare an annual summary report, which is to be submitted when requested by Health Canada. Thus, the PBRER may now be submitted to satisfy the requirement for an annual summary report.
Elsewhere, submission of PSURs has been mandatory in the EU since 2001 for all authorized products (Council Directive, 2001, p. 96), although the new pharmacovigilance legislation waives the obligation to submit PSURs routinely for generic medicinal products and well-established medicinal products (EMEA, 2013d, p. 7). Similarly, since at least 1996, the FDA has had the authority to require applicants to submit post-market periodic safety reports for each approved application, on a quarterly basis for the first three years following the US approval date and annually thereafter (US Government, 1996, sec. 314.80(2)).42

Both the EMA and the FDA also have the legislative authority to compel MAHs to prepare and submit post-authorization safety studies (EMEA, 2013b; FDA, 2011). The recently announced Bill C-17 proposes an amendment to the Food and Drugs Act that would allow Health Canada to require persons to provide information within their control for the purpose of assessing serious risks to health, and to require manufacturers to compile information, conduct new tests or studies, and/or monitor experience, for the purpose of obtaining additional information. Bill C-17 also proposes to authorize Health Canada to impose terms and conditions on market authorizations and to amend these terms and conditions when necessary.

**Implementing service standards for post-market activities**

As part of the effort to implement a standardized approach to post-market surveillance, MHPD has established performance targets for some of its post-market surveillance activities. For its targets related to adverse reaction reports, MHPD has set a goal to meet the standard in 95% of cases; for its targets related to other post-market activities, MHPD has set a goal to meet the standard in 90% of cases. Targets are currently under development for causality assessments, for the content development of risk communications, and for the dissemination of risk communications (MHPD, 2012b). See Appendix C for more information.

MHPD adopted unofficial performance standards for signal assessments, based on the number of workdays between the signal assessment being assigned and the assessment being approved, in April 2007. The service standard varied according to the signal’s assigned priority level: 200 working days for low-priority signal assessments; 130 working days for medium-priority assessments; and 80 working days for high-priority assessments. These performance standards became official in November 2011, but were subsequently adjusted in April 2012 to a single 130-day target. MHPD representatives indicated that these changes were made because of a decision in January 2012 to stop assigning priority levels to signals. They indicated that under the new system, green priority signals tend to be more quickly acted upon by, for example, being flagged for ongoing monitoring. A discussion of the timeliness of Health Canada’s post-market activities is in Section 6.7.

---

42 The US FDA recently announced that it would accept periodic safety reports in the PBRER format (FDA, 2013b).
Expanding partnerships and use of existing databases

Finally, Health Canada is emphasizing more active post-market surveillance by partnering with external organizations and using existing databases. For example, under the FCSAP, Health Canada initiated the development of the DSEN. The DSEN is being developed as a virtual network connecting centres of excellence across the country, led by a few primary centres with distinctive leadership in a thematic area of research methodologies and competencies (Risk Sciences International, 2012). The DSEN is expected to improve Canada’s ability to engage urgent research issues immediately after they appear and to provide national coordination for post-market surveillance, ultimately informing regulatory decision making.

MHPD is also examining the potential for using existing databases and electronic health records (e.g., provincial databases, Canadian Institutes for Health Information, Statistics Canada) as potential sources for studies to support surveillance and signal detection (MHPD, 2011b). Since 1996, MHPD has partnered with the Canadian Paediatric Society in the Canadian Paediatric Surveillance Program (CPSP), which collects data from over 2,500 paediatricians and paediatric sub-specialists monthly to monitor rare diseases in Canadian children (Canadian Paediatric Society, n.d.). The CPSP has grown from three conditions under study in the pilot year to 50 conditions currently under study (Canadian Paediatric Society, n.d.).

The US FDA’s Sentinel System is one model of active post-market surveillance using existing databases and electronic health records. Launched in 2008, the Sentinel System was required by legislative changes in the Food and Drug Administration Amendments Act (Section 905), which called for active post-market safety surveillance and analysis (FDA, 2008). The system is currently operating as a “Mini-Sentinel” pilot project involving over 20 partners. Key elements include active surveillance of post-market activity through assessment of routinely collected electronic health care data in response to FDA concerns; assessment of changes in the use of medical products in response to FDA regulatory action; use of a distributed data network in which data partners retain control over data, but use standardized computer programs within their institutions and share aggregated results; and quality control (e.g., testing and improving on statistical methods) (Mini-Sentinel, n.d).

Several external key informants encouraged Health Canada to coordinate the collection of pharmacovigilance data from other federal departments, as well as from provincial governments and other bodies, such as poison control centres. They also encouraged sharing of post-market data with regulators in other jurisdictions, since safety issues will come to light more quickly when a larger population is monitored; in turn, this will allow regulators to respond more quickly to health and safety risks.

5.4.7 Compliance and enforcement

Health Canada has taken a number of steps to strengthen compliance and enforcement. Challenges remain related to GMP reporting by product line.

While compliance and enforcement is often thought of as the final step in the drug regulatory process, Health Canada is responsible for monitoring compliance and enforcing the regulatory framework for biologics at both pre-market and post-market stages. To this end, the Inspectorate
conducts monitoring inspections of establishments to assess compliance with GMP, as well as monitoring inspections to ensure compliance with regulatory requirements relating to GCPs and GVPs, as well as for blood, CTO, and donor semen for assisted conception. Health Canada also conducts compliance verifications in response to specific complaints or identified risks. In the event of noncompliance, the Inspectorate clarifies what is necessary to achieve compliance, and may take enforcement action if the regulated party does not voluntarily undertake compliance measures (see the list below for a summary of available voluntary and enforcement measures).

**Available compliance and enforcement measures**

**Voluntary measures**
- Consent to forfeiture
- Product detention
- Product disposal
- Stop-sale
- Recall

**Regulatory/enforcement measures**
- Customs activities
- Injunction
- Prosecution
- Forfeiture
- Public warning or advisory
- Letters to trade and regulated parties
- Regulatory stop-sale
- Search and seizure
- Seizure and detention
- Suspension or cancellation of marketing authorization or product licence
- Refusal, suspension, or amendment of establishment licence
- Refusal or cancellation of registration
- Warning letter

Strengthening compliance tools and approaches, with a view to achieving increased industry compliance with the regulatory framework for drugs (biologics and pharmaceuticals), has been a key objective of Health Canada during the evaluation period. Activities in this area include implementing new authorities and tools for compliance and enforcement, strengthening inspections of clinical trials, and introducing a risk-based approach to GMP inspections, among others. Most recently, Bill C-17 proposed amendments to the *Food and Drugs Act* that would enhance Health Canada’s compliance and enforcement authorities.
Implementing new authorities and tools for compliance and enforcement

Both the Blueprint for Renewal and the FCSAP describe Health Canada’s intention to seek new legislative and regulatory authorities for compliance and enforcement, such as authorities to order corrective actions and modernization of the current fines and penalties framework (HPFB, 2007a). New administration and enforcement measures, including mandatory recalls of therapeutic products and federal power to recall the remaining stocks of a drug once it has been taken off the market due to safety concerns, as well as a modernized framework for monetary fines and penalties, were included in Bill C-51, which did not become law.

Bill C-17, which was announced on December 6, 2013, reintroduced similar amendments to the Food and Drugs Act as were originally included in Bill C-51. In particular, the proposed amendments would give Health Canada the power to recall therapeutic products from the market when they present an imminent or serious risk to health. The amendments also include increased fines and penalties up to a maximum of $5,000,000 and/or two years in prison. These amendments, if implemented, would address the concerns expressed by some key informants about what they perceive as the relatively limited enforcement options that are currently available to Health Canada.

Strengthening clinical trial inspections

Health Canada introduced a clinical trial inspection program in 2002 with the twofold objective of protecting the safety of trial participants and verifying the quality of clinical trial data. Under the inspection program, up to 2% of all Canadian clinical trials (including human drugs and biologies) are selected for inspection each year. Health Canada estimates that there are approximately 4,000 clinical trials underway in any given year in Canada; given a 2% target, this represents approximately 80 inspections each year. Site selection is based on risk criteria, including the number of clinical trials conducted at the site; the number of subjects enrolled; the number of serious unexpected adverse drug reactions at the site; and observations made during past inspections. Two ratings are possible: compliant or non-compliant.

In recent years, both the OAG and the Senate Standing Committee identified shortcomings in Health Canada’s approach to clinical trial inspections, including failure to collect regularly all of the information necessary to assess risk criteria for site selection, to meet the 2% target for inspections, and to set timelines for notifying sponsors of non-compliances (OAG, 2011; SSCSAST, 2012). In response, Health Canada has committed to publishing annual reports on its clinical trial inspections, has revised its inspection procedures to include timelines for key steps in the process, including notification of non-compliant ratings and review of proposed corrective measures, and has developed a risk-based process for selecting clinical trial sites for inspection. The risk-based criteria used to select sites for inspection include, but are not limited to, the phase in the drug development process, the complexity of the trial design, including its subject population, its level of risk to Canadians, novel therapies/dosage forms, significant or frequent

---

43 The sample is not weighted by product line.
reports of adverse events, notices from sponsors of protocol deviations, and emerging themes or trends (Inspectorate, 2013). According to Health Canada, other considerations, such as international best practices, may also be used.

Health Canada indicated that training on the new process was provided to Inspectorate GCP staff in May 2013 and TPD/BGTD reviewers in October 2013. The new process was implemented on June 1, 2013, with a phased-in approach using both the old and the new selection systems. Once fully implemented and documented, the risk-based process for site selection may help to address concerns expressed in interviews regarding a lack of transparency with respect to how clinical trials are selected for inspection.

A few external key informants expressed concern that the inspection program itself focuses on factors that in their view are irrelevant to the safety of trial participants or the quality of the research, or already subject to oversight from other sources.

**Enhancing drug establishment licensing and GMP inspections**

Establishments engaged in fabrication, packaging/labelling, testing, importing, distributing, and wholesaling of drugs are required to obtain a Drug Establishment Licence (DEL) in order to operate legally in Canada. To receive a DEL, an establishment must pass an assessment conducted by the Inspectorate, verifying compliance with Part C, Divisions 2 to 4 of the *Food and Drug Regulations*, which relate to Good Manufacturing Practices (GMPs). This includes requirements for the premises, equipment, personnel, sanitation, raw material testing, manufacturing, quality control, packaging material testing, finished product testing, record-keeping, sample retention, sterile product handling, and product stability (GoC, 2012d). GMP inspections of domestic establishments occur in cycles of 24 months for fabricators, packagers/labellers, and testing laboratories, and 36 months for importers, distributors, and wholesalers. New establishments that are applying for a DEL must be ready for an inspection when submitting the application, as the Inspectorate works to perform initial inspections within three months following the receipt of the request. A regular inspection follows the initial inspection within 12 months.

Domestic establishments are rated as either compliant (C) or non-compliant (NC) according to the risk given to observations noted during inspections (Inspectorate, 2012d). There are three levels of risk, with Risk 1 being the highest level of risk and Risk 3 being the lowest. If one or more observations are classified as Risk 1, the overall inspection rating may be NC.

Blood establishments are also currently required to obtain DELs and comply with GMPs. To become licensed, blood establishments must submit a file to the Inspectorate and concurrently to BGTD (HPFB, 2006). As part of the review process, BGTD may choose to conduct an OSE, potentially including a review of administrative documents, observation of establishment processes and demonstration of equipment, and an examination of establishment records (HPFB, 2006). GMP compliance is assessed at intervals depending on the establishment centre type and the complexity of activities performed there (Inspectorate, 2010b).
It is important to note that although Health Canada only recently extended the regulatory requirement for GMP to active pharmaceutical ingredients (Health Canada, 2013e), bulk process intermediates (BPIs) are covered under the GMP requirement in Division 2 Part C of the Food and Drug Regulations. Health Canada has provided specific guidance relating to GMPs for biologic drugs, as well as to blood and blood components.

Under the proposed Blood Regulations, authorization and establishment licensing will be required for establishments involved in processing allogeneic blood and blood components for transfusions, processing source plasma for drugs for human use, and importing blood for transfusion. Establishment registration will be required for establishments that collect blood or blood components for autologous use or perform transformation activities on blood or blood components determined safe for distribution or for transfusion.

**GMP inspections**

Over the period of the evaluation, Health Canada reviewed its domestic GMP inspection program, intending, in part, to improve effectiveness and create efficiencies that would allow it to attain stability in the program and avoid backlogs, which had been a significant problem spanning several years (Inspectorate, 2007). The review was also intended to align the GMP inspection program with the Inspectorate’s strategic plan, international changes in the regulation of drug quality, and the international harmonization of inspection programs.

Recommendations arising from the review addressed piloting risk-based inspections, inspections of establishments with many sites, and “targeted add-on to inspection” (Inspectorate, 2012b, p. 6). Since the review was completed, Health Canada has made a number of changes to the GMP inspection program. Health Canada piloted a PIC/S risk-based inspection scheduling model in fiscal year 2011–2012, and, following pilot exercises, inspection procedures and policies were revised to facilitate implementation of the model. Revisions to the inspection procedure and/or policy include the following:

- revised inspection frequencies to better address situations of less risk such as lower risk labelling activities
- enhanced inspection frequencies to address situations of higher risk
- processes to enhance consistency in providing written and electronic notification of announced inspections
- risk criteria for inspection intervals between an initial GMP inspection and the subsequent regular GMP inspection (up to a maximum of 12 months)
- risk criteria for selection of products and processes for documentation review
- risk criteria for targeted sampling
- basic risk assessment tools to determine risk control measures during a GMP inspection, including assignment of rating and needs for an enhanced inspection frequency.

---

44 Under the revised framework, an enhanced inspection frequency is a decrease in the time before the next inspection, which could be from a short period up to two years depending on risk. Enhanced inspection frequencies apply to situations where significant deficiencies to regulatory obligations are identified or circumstances where the Inspectorate requires increased inspection oversight for risk mitigation strategies such as might exist for establishments with highly complex activities or highly critical products.
Health Canada also revised its policy stipulating that upon expiry, a new licence would not be issued unless the previous inspection was within time frames defined in policy. Removing the expiration date from the license aligned Health Canada with international approaches, with the added benefit that the license would remain valid without worry of expiration even if the last inspection was not within the time frame defined in policy.

In recent years, Health Canada has also made progress in eliminating the backlog in GMP inspections and approaching the annual target number of inspections. In 2008–2009, the Inspectorate had a backlog of 210 inspections and conducted 64% of its target number of inspections. Since then, the backlog has been reduced and the proportion of targeted inspections completed has increased, albeit not steadily. In 2011–2012, 98% of targeted inspections were completed, while the following year, 90% of the targeted inspections were completed.\textsuperscript{45} The backlog in 2012–2013 was 34 inspections. These improvements may be due, in part, to an increase in the number of GMP inspectors under the CRI. See Appendix C for more detailed information.

The move toward risk-based inspections is consistent with the approach taken internationally. External key informants noted that the adoption of a risk-based approach to compliance and enforcement means that Health Canada may be less likely to respond to issues perceived as presenting a low risk to consumers. Furthermore, while risk-based approaches to enforcement and compliance are appropriate in a context of limited resources, they do not necessarily provide a strong understanding of compliance across the regulated industry as a whole, nor are they always well-equipped to identify new or emerging risks (Sparrow, 2000, p. 290).

An initiative launched in December 2011 between Canada and the US under the Regulatory Cooperation Council (RCC) aims to address the challenges associated with GMP inspections, by increasing each country’s reliance on GMP inspection reports of drug manufacturing facilities prepared by the other country, rather than unnecessarily duplicating efforts (RCC Personal Care Products and Pharmaceuticals Working Group, 2012). The main activities included in the work plan are routine exchange and assessment of inspection reports between the countries and regular engagement of stakeholders through web postings and quarterly meetings. The countries ultimately intend to develop a framework to assure reliance on each other’s inspection reports, which could include: a joint GMP database to standardize the exchange of inspection reports; routine sharing of inspection reports and significant regulatory actions/changes; joint inspections of selected establishments; and a forum in which to have discussions and adjust to regulatory changes by either country.

Despite the focus in the GMP workplan on standardizing and sharing of inspection reports, Health Canada and the FDA currently differ in their reporting approaches. While the FDA reports based on the centre responsible for regulating various categories of product — reporting inspection data separately for the Center for Veterinary Medicine (veterinary drugs), the Center for Drug Evaluation and Research (human drugs), and the Center for Biologics Evaluation and Research (biologics) (FDA, 2013c) — Health Canada aggregates GMP reporting for

\textsuperscript{45} Calculation of the proportion of the target number of inspections includes inspections that were removed from the plan due to establishment inactivity or other reasons for withdrawal as part of the total number of completed inspections, although no inspections were conducted in these cases.
pharmaceutical, biologic and veterinary drugs. Health Canada indicated that this approach is taken because its approach to GMP inspections is facility-based and that it is currently not possible to track inspections by product line. Nonetheless, achieving the objectives of the GMP work plan may require a common approach to compliance reporting.

Foreign sites that manufacture drugs for import into Canada by Canadian manufacturers are, like domestic sites, subject to GMP requirements. While in the case of biologics these are inspected as part of OSEs, the Inspectorate seldom conducts foreign site inspections. Rather, the Inspectorate assesses the initial application for a foreign-site DEL, and the GMP compliance of foreign sites, based on evidence provided by the sponsor. The evidence that must be provided differs depending on whether or not the site is located in a country with which Health Canada has a Mutual Recognition Agreement (MRA), which is an agreement between Health Canada and another country on the equivalence of their respective GMP compliance programmes (Health Canada, 2009a). Canada currently has MRAs with the European Community, Switzerland, Iceland, Liechtenstein, Norway, and Australia (Inspectorate, 2012f). However, Health Canada estimates that 76% of the drug products imported into Canada come from countries with which it does not have an MRA; in the past five years, the Department has undertaken 35 inspections of foreign sites (Cassels, 2012). Inspectorate representatives confirmed that this number includes inspections involving both pharmaceutical and biologic drugs.

The lack of GMP inspections of foreign facilities in countries with which Canada has not signed an MRA – in particular, China and India – was a concern for some key informants, who worried about the potential for Canadians to be exposed to low-quality or counterfeit health products. According to BGTD, at the present time none of the manufacturers licensed to sell biologics in Canada are located in China or India. Rather, all are located in Canada, Europe, the US, and Israel.46

**Implementing registration and inspection of CTO establishments**

While CTO establishments do not require an establishment licence and are not required to comply with GMP, the CTO Regulations introduced a requirement for these establishments to register with Health Canada if they are a source establishment for CTO, if they distribute CTO to others within Canada, or if they import CTO for further distribution (HPFB, 2009). Based on the focus group with CTO establishments, the registration process is seen as reasonably straightforward, although some concerns were expressed that certain establishments, such as marketing agents and small health care institutions, are not registered and thus may be contributing to potential safety issues.

As is also the case for other products, a predetermined, risk-based inspection cycle exists for CTO establishments to determine their compliance with regulations. Health Canada began inspecting CTO establishments to assess their compliance with the regulations in August 2009. Health Canada has taken a number of steps to promote awareness of and compliance with the CTO Regulations, including the following:

- publishing a guidance document in support of the CTO Regulations

46 Heparin, which is manufactured in China and was regulated as a pharmaceutical until 2008, is the sole exception.
• developing a Pre-Inspection Package to provide further information and clarification on Health Canada’s inspections
• developing and distributing several FAQ sheets to increase stakeholder awareness of the regulatory requirements
• holding information sessions across the country to promote compliance, with the goal of increasing awareness of regulatory requirements and creating a forum in which stakeholders could build relationships.

From the perspective of participants in the focus group with CTO establishments, the quality of the inspections is variable. Participants reported that while some inspectors are highly-qualified and familiar with the particular CTO industry they are inspecting, others are not, with the result that they sometimes focus on issues irrelevant to product safety. In a related vein, participants also noted that inspections tend to be very “paper-based.” This was contrasted to CTO inspections performed by the FDA, whose inspectors, according to participants, spend more “hands-on” time in establishments observing processes and procedures. Participants recommended that Health Canada improve the inspection process by establishing greater consistency and standardization in the inspection process and improving the training and industry-specific knowledge of inspectors. The group suggested that one way to do this would be to use inspectors who have experience in the relevant CTO industry.

Key informants representing the Inspectorate noted the following:

• All inspectors within the Blood, Tissues, Organs and Xenografts (BTOX) unit have a science degree at the B.Sc. level or higher.
• Many BTOX inspectors have more than 10 years of experience as BTOX inspectors.
• The Inspectorate provided extensive training to inspectors prior to the coming into force of the CTO Regulations.
• At least one or two inspectors attend international conferences every year.

Inspectorate representatives also noted that to promote consistency in delivery of a national compliance and enforcement program, since the start of CTO inspections in 2009, deficiencies identified during the inspections are reviewed in a joint BP meeting (involving the Inspectorate, MHPD and BGTD) prior to issuance of the inspection reports. The purpose of these information-sharing meetings is to ensure consistency in interpretation and application of the CTO Regulations and a common understanding of the law.

**Other initiatives to strengthen compliance and enforcement**

Finally, Health Canada has undertaken several other initiatives to strengthen compliance and enforcement of the regulatory framework for human drugs, including biologics and pharmaceuticals.
• **Introducing post-marketing reporting inspections.** In 2004, Health Canada introduced the Post Market Reporting Compliance Program (PMRC) with the objective of “verify[ing] manufacturers are in compliance with the regulatory requirements for the receipt, analysis, and submission of drug safety information to Health Canada” (Inspectorate, 2012a, p. 2). In 2013, the program was renamed as the Good Pharmacovigilance Practices (GVP) inspection program; Health Canada representatives reported that this change was made in order to more closely align with international regulators. In February 2013, a risk-based approach for inspection scheduling was implemented, along with new guidance for industry.

• **Strengthening oversight of imported products.** Health Canada strengthened regulatory oversight of imported products by developing the National Border Integrity Program in collaboration with the CFIA, the CBSA, and the FDA. The objective of the Border Integrity Program is to strengthen Health Canada’s ability to make and support admissibility decisions at the border relating to health products. Pillars of the program include the authority to inspect and take samples of health products intended for importation, request the CBSA to target and detain shipments for an admissibility determination, and engage in compliance and enforcement action; use of partnerships and best practices; awareness and education activities; and efficient use of information technology through participation in the Single Window Initiative led by the CBSA, which is intended to create an automated, risk-based approach to identifying high-risk goods and accelerating the flow of low-risk goods (Inspectorate, 2010a).

• **Developing a policy on counterfeit health products.** In a related initiative, Health Canada issued a policy on counterfeit health products in 2010, the primary objective of which is “to manage the risk to Canadians and to have the counterfeit product removed from market using the most appropriate level of intervention and notifying parties at risk” (Inspectorate, 2010c). According to Inspectorate documentation, an Anti-Counterfeit Strategy and phased implementation plan have been developed; an Anti-counterfeit Taskforce has been created; and the Inspectorate and the RCMP have collaboratively developed a Memorandum of Understanding (MOU) (Inspectorate, 2009, p. 24).

#### 5.4.8 Communications and stakeholder engagement

Health Canada has undertaken a number of initiatives to improve communications and stakeholder engagement.

The preceding sections described Health Canada’s activities in relation to the four main stages of the regulatory process: clinical trials, submission review and market authorization, post-market surveillance and monitoring, and compliance and enforcement. Throughout the process, Health

---

47 The Inspectorate and RCMP set out an agreement in principle with respect to collaborative information-sharing between the parties that set the stage for the development of the Inspectorate's *Information-Sharing Policy* (POL-0103) and *Information-Sharing Legal Opinion Chart* (GUI-0106), which together provide administrative structure to the Inspectorate's information-sharing process in a manner that respects legal constraints such as statutory and Charter-based privacy laws. For example, this may include sharing of information relating to specific regulated persons, when linked to information about regulated activities and/or products such as importations of suspected counterfeit drugs). These documents are intended to be evergreen, updated from time to time to incorporate new case law, emerging concerns, and changes in Inspectorate activity.
Canada also communicates and engages with stakeholders such as consumer/patient organizations, health care providers and industry. Over the evaluation period, Health Canada has pursued two main objectives in relation to stakeholder communications and engagement: providing Canadians with more information on health products, including more timely and accessible information, and making the regulatory system more open to consumer and other stakeholder input and involvement. Its activities in these areas are described below.

**Enhancing the transparency of the drug review process**

Consistent with its objective of providing Canadians with more information on health products, Health Canada launched the Summary Basis of Decision (SBD) initiative in 2005 to enhance the transparency of the drug review process. SBD documents provide health care professionals, consumers, and patients with the scientific and benefit/risk-based considerations involved in granting market authorization. Between 2005 and September 2012, a total of 47 SBDs were released for biologics.

An evaluation of the first phase of the initiative, along with the OAG’s 2011 report on regulating pharmaceuticals, resulted in several changes in Phase II, including reducing the target time for SBD publication, limiting the ability of MAHs to request changes and to appeal the SBD, introducing a Q&A format and more information on Health Canada’s risk/benefit analysis, and publishing a post-authorization activity table (PAAT) for eligible products (TPD, 2012). Phase II of the SBD project applies to new drugs involving new active substances, as well as SEBs authorized after September 1, 2012.

The PAAT was introduced in part to address the OAG’s concerns that Health Canada was failing to disclose information related to NOC/cs, rejections, and withdrawals of new drugs (OAG, 2011, p. 18). PAATs provide ongoing information about approved products. They include a brief summary of activities that affect the safe and effective use of the product, such as information related to submissions for a new use of the product (whether Health Canada’s decision was positive or negative), submissions filed in order to meet conditions (for products approved under the NOC/c Guidance), and regulatory decisions such as the cancellation of the DIN.

To date, Health Canada has not introduced SBDs for negative decisions — although it has indicated that it may consider this in future (TPD, 2012, p. 1). Some external key informants stated that in their view, Health Canada releases relatively little information about the pre-market review process to the public. They noted that Health Canada does not provide information about what drugs are currently under review; it provides relatively little information about how the review was carried out and what the reviewers concluded about the products in question; and it provides no information on pipeline meetings with industry.

By comparison, the FDA’s Drugs@FDA website provides a searchable database containing documentation relating to approved brand-name and generic prescription and OTC human drugs and biological therapeutic products, consisting of the entire drug approval package (including the

---

48 Meetings held between industry representatives and Health Canada to exchange information on emerging issues, upcoming submissions, etc. The resulting information is used by Health Canada for planning (e.g., workload forecasting).
FDA’s complete review reports, as well as approval letters, though not the submissions (themselves) and all versions of product labels for products approved since 1998. However, a summary document such as the SBD does not appear to be available (FDA, 2013a). In the EU, the EMA publishes a European Public Assessment Report (EPAR) for every medicine granted a central marketing authorization by the European Commission. The information available includes a summary in Q&A format and the package leaflet. Information is also provided on medicines that have been refused a marketing authorization or that have been suspended or withdrawn after being approved (EMEA, 2013e).

In October 2013, the Minister of Health told the Toronto Star that she has asked Health Canada to “take the steps necessary to begin publishing drug reviews transparently to ensure Canadians and medical professionals have the information they need and want” (Toronto Star, 2013). Consultations with stakeholders have taken place and MHPD is planning to release the first drug safety review in the near future. Current plans are to publish a brief summary of the safety review (three to five pages), although the full report will be available on request. A phased approach will be taken to implementation, with Phase 1 focusing on high visibility/high interest drugs (with specific criteria to be developed) and Phase 2 focusing on all safety reviews that result in the need for risk minimization actions; in Phase 3, “information on all reviews could be published” (Health Canada, 2014). It is important to note that this initiative involves safety reviews completed post-market, not safety reviews done as part of the pre-market review process.

Finally, it should be noted that Health Canada, unlike the FDA, does not provide the public with updates on progress made by sponsors in fulfilling post-market conditions. External key informants suggested that if issues associated with a drug are serious enough to merit attaching conditions to approval, Health Canada should be enforcing their fulfillment, as well as reporting to the public on sponsors’ compliance with conditions. The evaluation could not determine the extent to which Health Canada currently monitors sponsors’ compliance with conditions imposed with NOC/cs.

Enhancing drug product labelling

Health Canada has undertaken several initiatives to improve the quality and availability of easy-to-understand drug product labelling. Drug product labelling refers to the product monograph, materials included in the product’s packaging, and materials supplied to the consumer at the time of purchase. This includes package labelling, leaflets, fact sheets, and any other material containing drug product specific information (TPD, 2011). Having access to clearly-written and accurate drug information is important because it enables health professionals and consumers to make informed decisions about drug therapies (TPD, 2011). Initiatives in this area relevant to biologics include the following:

- **Introducing enhancements to the product monograph.** A product monograph is a factual, scientific document that includes information on the drug’s properties, conditions of use, and any other information required for optimal, safe, and effective use. A review of the product monograph is part of the drug submission review process, and an NOC is not given if a product monograph is not available. The product monograph consists of three sections, each aimed at different audiences: health professionals, scientific professionals, and (since 2004) consumers (TPD, 2008). In 2008, as part of the FCSAP, Health Canada began publishing product monographs, including the consumer portion, on its website through the Drug Product...
Introducing regulatory amendments concerning labelling, packaging, and brand names of drugs for human use. Most recently, in June 2013, under the Plain Language Labelling Initiative — a component of Phase I of Health Canada’s plans for regulatory modernization — proposed amendments to the labelling requirements under the Food and Drug Regulations were published in Canada Gazette. The proposed regulations would introduce a general requirement for drug labels to use plain language and a format or presentation that does not impede comprehension. They would also introduce a number of new pre-market requirements, including listing of additional company contact information for consumers who experience a problem with the product; submission of mock-up labels and packaging as part of the pre-market submission process; and codification of current policy on look-alike/sound alike (LASA)\textsuperscript{50} products (GoC, 2013b).

Similar requirements for plain language labelling have been implemented elsewhere. The EU implemented requirements for standardized, easy-to-read labelling over a decade ago. Directive 2001/83/EC indicates that labelling for all medicinal products must be “easily legible, clearly comprehensible, and indelible,” follow a mandatory EMEA format to ensure consistency, and provide full colour mock-ups for review (EMEA, 2009). In the US, the FDA introduced the Physician Labelling Rule (PLR) Requirements in 2006 for prescribing information (i.e., package inserts), which sought to enhance the safe and effective use of prescription drug products by giving health care professionals clear and concise information that was easier to access, read, and use (FDA, 2013d). The PLR Requirements regulation requires the prescribing information to have specific pieces of information in summary “highlight” format.\textsuperscript{51}

The proposed regulations would align Health Canada with its international counterparts in requiring easy-to-understand product labels. Nevertheless, Health Canada currently has limited ability to require a manufacturer to modify a product monograph or label once a product has received an NOC (TPD, 2011). This shortcoming is addressed by Bill C-17, which would give Health Canada the authority to require manufacturers to modify a product’s label or to modify or replace its package in order to prevent injury to health.

---

\textsuperscript{49} According to information provided by Health Canada, product monographs are posted on the DPD generally 24 hours after an NOC is granted. However, they are visible to the public only once the company notifies Health Canada that it intends to market the product in Canada. A company has 30 days to notify Health Canada once they market a product. Once Health Canada receives notification, the product monograph is made visible to the public. This is typically done within 24 to 48 hours of receipt of notification.

\textsuperscript{50} Look-alike Sound-alike (LASA) health product names are “names of different health products that have orthographic similarities and/or similar phonetics (i.e. similar when written or spoken)” (HPFB, 2005a, p. 1). LASA health products create risks due to the possibility of confusion and errors in prescribing, dispensing, or administering the product. The proposed regulatory amendment would require manufacturers to submit an assessment of the drug’s brand name, showing it is not likely to be mistaken for another drug (GoC, 2013b).

\textsuperscript{51} This information includes product name, boxed warning, recent major changes, indications and usage, dosage and administration, contraindications, warnings and precautions, adverse reactions, drug interactions, and use in specific populations.
By comparison, the FDA has the authority to require product labelling to be updated as new safety information becomes available about the drug (US Government, 2012b). For example, the FDA has the authority to require a boxed warning to be placed in both the summary of prescribing information (highlights) and in the full prescribing information pamphlet; the boxed warning contains a bold text warning that the drug may cause serious injury or death and provides a brief explanation of the risk before referring readers to the appropriate section of the prescribing information pamphlet for more information (US Government, 2012a). Thus, the FDA uses the label’s boxed warning as a tool to communicate safety and risk information to physicians (FDA, 2010).

Similarly, the EU’s new pharmacovigilance legislation requires medicines that are subject to additional post-market monitoring to include an inverted black triangle on the drug product’s leaflet, along with statements indicating that the product is undergoing additional monitoring and encouraging patients to report adverse reactions (EMEA, 2013c). The symbol and statements are included on biologics, biosimilars, and pharmaceuticals containing new active substances authorized as of January 1, 2011, as well as on products undergoing post-authorization safety studies, or products that are subject to conditions or restrictions on safety and efficacy, as per a risk management plan (European Parliament, 2010a, 2010b).

Enhancing post-market safety and risk communications

Since 2005, the MedEffect website has been Health Canada’s main mechanism for communicating post-market safety and risk information to health professionals and the public and for enhancing communication to health professionals by providing a central repository of this information. The MedEffect Canada Initiative was created to improve access to safety information and adverse reaction information for marketed health products, while also providing a single window approach to post-market surveillance activities. The single window approach is intended to provide the public and health professionals with centralized, easy-to-find information online, with the goal of increasing awareness of the importance of reporting adverse events related to health products, while also making it easier for health professionals and members of the public to report adverse events.

Until recently, Health Canada published safety and risk information regarding health products on the “advisories, warnings and recalls” link on the MedEffect website. Other distribution methods were and are still used, including mail-outs and hard copy publications, dissemination to professional associations to encourage posting on their website and publication in their journals and newsletters, and distribution to licensing bodies, provincial ministries, and foreign regulatory agencies. In addition, the free MedEffect e-notice delivers advisories, warnings, and recalls; the quarterly Canadian Adverse Reaction Newsletter; and MedEffect content updates directly to approximately 20,000 subscribers. To communicate product safety risks, Health Canada uses a variety of risk communications documents, targeting the public and health professionals and intended for high-, medium- and low-risk situations.

According to data provided by MHPD, between 2005-2006 and February 28, 2013, there were 148 risk communications related to biologics posted on the MedEffect and Healthy Canadians web sites. Analysis of communications posted on MedEffect revealed some limitations
associated with the risk communications. For example, communications concerning product recalls did not always clearly identify whether a product recall was being communicated. Furthermore, until recently, information on product recalls was available in two locations on Health Canada’s website: on MedEffect’s “advisories, warnings and recalls” site and on the Drug Recall Listing, leading to the potential for confusion and inconsistency in the information posted on the two sites.52

In February 2013, Health Canada launched the Recalls and Safety Alerts Database, a revised system for disseminating risk communications to health professionals and the public (Health Canada, 2013c).53 The new database seems to be an improvement over the “advisories, warnings and recalls” listing on MedEffect in several ways, including the availability of an advanced search feature and a new format for risk communications. All risk communications are now classified into one of two main categories — advisories and recalls — which should eliminate any uncertainty as to whether or not a product recall is being communicated.54 Even more recently, in mid-March 2013, Health Canada eliminated the online Drug Recall Listing and consolidated product recall information on the Recalls and Safety Alerts Database. This change has eliminated the potential for inconsistency, though there is no longer a complete listing of recalls of all health hazard types available on Health Canada’s website.

To further improve the risk communications process, MHPD indicated that it is currently in the process of reviewing its existing performance targets for the content development of risk communications and for the dissemination of risk communications, which are contained within its guidance document for industry on the issuance of risk communications. The guidance indicates that health professional communications “should be developed and disseminated within 12 working days after the date on which the Request Letter is received” and that the accompanying public communication “should be issued 3 working days after the issuance” of the health professional communication (Health Canada, 2010a, p. 7). The Request Letter refers to a letter sent by Health Canada to the MAH, outlining the nature of the safety issue and requesting the MAH to draft risk communications for health professionals and the public. MHPD indicated that there is currently no specific timeline for the issuance of the Request Letter; this depends on the nature of the risk. MHPD also indicated that the 12-day timeline is based on two drafts of the health communication, whereas the current requirements are for three drafts. Since 2011, the performance standard for issuing a health professional communication has been 26 days.

52 Until recently, all drug recalls, regardless of type, were posted on the Drug Recall Listing, and some resulted in a risk communication posted on MedEffect. Health Canada guidance states that “[n]otices/advisories from companies may be posted on MedEffect when Health Canada deems that it is important to have the detailed safety information available for everybody who may need to know it” (Health Canada, 2008c, p. 29). Attempts by the evaluation to quantify the Type I recalls in the Drug Recall Listing that resulted in a MedEffect communication were ultimately abandoned, due to methodological difficulties.

53 These initiatives are in response to a Federal Court ruling that all federal government sites must meet international standards for accessibility, as well as a directive from Treasury Board to reduce the number of pages on the website by half by July 31, 2013 (Health Canada, 2013f).

54 In some instances both a recall and an advisory may be issued. MHPD indicated that in a minority of recalls, it may be necessary to provide additional information about the risk and what to do about it. In these cases, in addition to the recall posting, an advisory will be issued. There may also be situations where the recall posting is deemed inadequate to reach the target audience and a related advisory may be issued as supplementary distribution in order to reach specific groups (e.g., to hospitals if recall affects a hospital-only product).
Additionally, MHPD indicated that Health Canada is looking at areas where more focused improvements in risk communications could be made. Finally, HPFB is drafting internal guidance on the risk communication process for human health products, detailing the process(es) to be followed and the responsibilities of the parties involved, including the science directorates (TPD or BGTD), the Inspectorate, MHPD, the Communications and Public Affairs Branch (CPAB), the MAH, and the Assistant Deputy Minister (ADM) (Health Canada, 2013i).

**Opening the regulatory system to stakeholder input and involvement**

In accordance with the established process for regulatory development at the federal level, Health Canada conducts public consultations on proposed amendments to the *Food and Drug Regulations* and other related regulations. Health Canada has also undertaken several initiatives to make the regulatory system more open to stakeholder input and involvement. Some examples are listed below.

- Developing a Public Involvement Framework in 2005, following internal and external consultations with industry, patient and consumer groups, as well as academia and health professionals. The framework is intended to guide public involvement activities across all of the Branch’s responsibilities (HPFB, 2005b, p. 1).

- Developing, in 2007, a policy on public input into the review process for regulated products that is intended to resolve shortcomings in the old regulatory framework, which put the onus on manufacturers to provide all information on a product submitted for approval and did not explicitly allow information from consumers, patient groups, physicians and others to be considered in the decision-making process. The policy sets out the processes to be used when the Branch “identifies a situation where decision making regarding a regulated product would benefit from public input “(HPFB, 2007b, p. 1). The policy also states the Branch would make public (via the Health Canada website) reports on the input received from the public. Such reports would state the objectives and methods of the public input and provide an overview of the input received (HPFB, 2007b, p. 16). Finally, the policy provides a definition of confidential business information and outlines HPFB’s treatment of such information (HPFB, 2007b).

- Establishing Expert Advisory Committees (EACs) and Expert Advisory Panels (EAPs) to provide policy guidance and advice on specific scientific issues, respectively. Some examples include the Expert Advisory Committee on the Vigilance of Health Products (EAC-VHP), which provides HPFB with external expertise on post-market surveillance, risk communications, and regulatory advertising oversight (MHPD, 2008); the Paediatric EAC which provides expert advice and public involvement in the development, licensing, and continued vigilance for health products on the market destined for children, pregnant and nursing women” (Health Canada, 2012i); and EACs that were consulted on specific issues relating to the blood and CTO regulations.

- Conducting public, stakeholder, and industry consultations on draft guidance and proposed policies (in addition to consultations on proposed regulatory amendments).
• Meeting regularly with industry and other stakeholders through the Bilateral Meeting Program (BMP). Through these meetings, BGTD meets regularly with industry and other stakeholder associations; the meetings also often involve participation from other HPFB directorates and are an opportunity for stakeholders to discuss and consult on regulatory issues of mutual interest, exchange information, and share expertise. Associations involved in BGTD’s BMP include BIOTECanada, BIOTECanada Vaccine Industry Committee, and the Nuclear Medicine Alliance. Topics include submission review performance, compliance activities, cost recovery, proposed regulatory changes, and development of new guidance documents.

• Posting information for industry on the application and review process for biologics, along with associated policies and guidance documents.

• Holding pre-submission meetings with sponsors prior to their filing an NDS or CTA.

• Conducting compliance education and promotion activities, such as road shows and presentations, to inform industry of its obligations.

An Office of Public Ombudsman, created under the TPSI to provide responses to public and stakeholder complaints on regulatory issues (Health Canada, 2006, p. 9), is no longer in existence. However, there is now a Food and Drugs Act Liaison Office (FDALO) whose role is to “improve relations between external stakeholders and representatives of Health Canada, as well as to increase the openness and transparency in the regulatory process” (Health Canada, 2012e). The FDALO acts as an impartial and confidential resource for receiving complaints, concerns or enquires from individuals, businesses, and organizations. According to the FDALO’s activity report for 2011–2012, the office opened 163 cases in that year, of which 55% were information-seeking cases, while the remaining 45% were issues management cases (Health Canada, 2012f). While there were no cases involving BGTD, it is not known if there were any cases related to biologic products.

Some external key informants believe that the stakeholder consultation and engagement process may favour industry over consumers, patients, and health care practitioners. It was noted that industry may be most likely to be aware of consultation opportunities because of its strong interest in how its products are affected by policy or regulatory changes, and may have greater resources to participate than other stakeholders, particularly in cases where travel is required.55 The evaluation could not determine whether industry participates more often than other stakeholder groups in public consultations. Industry does have opportunities to consult with Health Canada through the BMP and through pipeline and pre-submission meetings, which are not available to consumers, patients, or health care practitioners.

---

55 Health Canada does not pay participants’ travel expenses, with the exception of EAC and EAP members.
6.0 Findings – outcomes achieved

This section presents the findings with respect to the evaluation questions on outcomes. While Health Canada has engaged in many activities that should produce the expected outcomes, data to support a definitive conclusion regarding the extent to which expected outcomes have been achieved are relatively limited. For this reason, the evaluation findings pertaining to program outcomes should be considered as a baseline.

6.1 Stakeholder awareness and understanding

There are opportunities to improve awareness and understanding of drug safety information among consumers and health professionals.

In the short term, Health Canada’s activities, and in particular its communication and stakeholder engagement activities, are expected to produce increased awareness and understanding by non-industry stakeholders (i.e., consumers and health professionals) of risks and benefits related to biologics. Some relevant information is available from a series of studies sponsored by Health Canada since 2003. Overall, these studies suggested opportunities to improve awareness among both consumers and health professionals of drug safety information available from Health Canada, although results are not disaggregated by product type (biologic or pharmaceutical drugs). For example, the studies found the following:

• In both 2003 and 2006, about one third of consumers were aware that new drug safety information was available through Health Canada’s website. However, only about 10% had accessed this information within the last six months. Conversely, about two thirds were aware of advisories and warnings issued through the media (Decima Research, 2003, 2006). Very few respondents (1%) had subscribed to the MedEffect e-Notice (Decima Research, 2006).

• In 2003, just over half of health professionals were familiar with both Dear Health Professional Letters (DHPLs) issued by manufacturers and the Canadian Adverse Reaction Newsletter, but fewer were familiar with Health Canada-issued DHPLs, Health Canada’s online drug safety advisories, and Health Canada’s electronic mailing list (Decima Research, 2003). In 2007, 12% of health professionals identified Health Canada/MedEffect as a source for new drug safety information (Environics Research Group, 2007). A qualitative study completed the same year found that very few health professionals were aware of the MedEffect website, and only one had subscribed to the e-Notice (The Antima Group & TNS Canada, 2007).

56 The studies examined public and medical professionals’ perceptions of drug safety in general, and Health Canada’s drug safety information in particular, assessing respondents’ information-seeking practices, awareness of information sources, and satisfaction with these information sources.
In both 2003 and 2007, about half of health professionals reported being familiar with how to report an adverse reaction. Pharmacists, and to a lesser degree, physicians, tended to be familiar with this process, while nurses, naturopaths, and dentists tended to be unfamiliar (Decima Research, 2003; Environics Research Group, 2007). Similarly, the 2007 qualitative study found a lack of awareness among health professionals on how and why adverse reaction reports should be made, and who should be making these to Health Canada (The Antima Group & TNS Canada, 2007).

See Appendix C for a more detailed summary of the findings from these surveys.

Since these studies were completed, Health Canada has not conducted any further research into the effectiveness of its risk communications or the information it provides to stakeholders. The survey of stakeholders was intended to fill this gap, but due to methodological limitations and a poor response rate, the results are unreliable and are not included in this report. As a result, information is limited to that obtained from external key informants, who generally did not express strong views of Health Canada’s risk communications or the other information Health Canada provides to stakeholders. They did, however, identify a number of issues and/or suggestions for improvement, as summarized below.

External key informant perceptions of Health Canada’s communications and information

- Risk communications may be too technical for some members of the public to understand.
- Risk communications could provide more detailed information for both health care practitioners and patients.
- Risk and safety information should be released to the public in a more timely fashion.
- Health Canada’s website is difficult to navigate and search; the design could be improved by creating separate pages for consumers and health care practitioners or improving links within the website.
- Web postings, while necessary, are not in themselves sufficient for communicating with stakeholders; Health Canada should expand its information dissemination activities through increased use of social and conventional media.
- Health Canada should provide more information to the public regarding pre-market reviews and analysis of adverse reaction reports.

Health Canada has recently undertaken to follow through on its long-standing commitments (dating to at least 2007) to assess the effectiveness of its health product risk communications. The Evaluation of the Effectiveness of Risk Communications project will evaluate the effectiveness of Health Canada issued/endorsed Dear Healthcare Professional Letters, Notices to Hospitals, and public communications over a one-year period between September 1, 2011 and September 1, 2012 (Health Canada, 2013g). The scope of the project covers risk communications
on pharmaceuticals, biologics, and medical devices, and includes an evaluation of 14 methodologies for future use in the evaluation of risk communications in terms of their reach, clarity and impact. The evaluation is expected to be completed in March 2014.57

6.2 Industry awareness and understanding

There are opportunities to improve awareness and understanding of pre-market activities among industry.

In the short term, Health Canada’s activities are expected to produce increased awareness and understanding by industry stakeholders of the regulatory frameworks for biologics. As described earlier in this report, industry has opportunities to provide input into proposed regulations and policies through Health Canada’s online consultation process and through the Government of Canada’s gazetting process for proposed new regulations, as well as opportunities to consult with Health Canada through the BMP and through pipeline and pre-submission meetings.

In the absence of baseline data, the available evidence does not support conclusions on the degree to which industry awareness and understanding may have increased, although it does point to some potential gaps in understanding and/or areas for improvement.

• **Submission requirements.** Most respondents to the biologics industry survey indicated that their firm has a strong understanding of Health Canada’s submission requirements for market approval. Qualitative information from the interviews with industry suggests that in some areas, greater clarity may be required. In particular, industry key informants identified a need for clearer guidance or information with respect to combination products, classification of emerging health products, and Health Canada’s use of foreign reviews and foreign guidance in the drug review process. Industry also perceives a need for greater clarity with respect to naming of SEBs, classification of CTO products, classification of some combination products, and regulation of stem cell and other emerging biologic therapies.

• **Adverse reaction reporting requirements.** A majority of respondents to the biologics industry survey believe that Health Canada has clearly outlined the instructions and requirements for adverse reaction reporting and defined what reactions must be reported, and agreed that the mandatory reporting forms are clear and understandable. Most also agreed that their firm could provide the required information and complete the report in the required time frame. However, participants in the focus group with CTO establishments described a lack of clarity around adverse reaction, error and accident reporting requirements and risk mitigation steps for CTO, and identified a need for clearer definitions and guidelines for reporting.

57 According to the PMEP, evaluation methods will include analysis of the timeliness and readability of Health Canada’s risk communications; website analytics; comparisons of the degree to which Health Canada’s approach (timeliness and messaging) is consistent with that of other regulators; a pop-up survey of users of the MedEffect website; analyses of prescribing trends and adverse reaction reporting trends; focus groups with users to explore attitudes, opinions, and satisfaction levels; and a survey of Canadians to examine similar issues (Health Canada, 2012j).
• **Other requirements.** Most respondents to the biologics industry survey reported that their firm has a strong understanding of Health Canada’s requirements relating to GMPs, establishment licensing, and regulatory compliance activities and related enforcement actions. In addition, a majority of respondents to the biologics industry survey reported a strong understanding of requirements under the Lot Release Program (LRP) and rated their understanding of GCP requirements as strong.

Industry key informants and survey respondents were generally satisfied with the information provided by Health Canada. A few external key informants recommended that Health Canada reduce its reliance on industry associations as a means of conveying policy and regulatory information to manufacturers, since firms that are not members of industry associations will tend to be excluded.

### 6.3 Safety and effectiveness

**There are pre-market and post-market processes in place that are intended to help ensure that biologics are safe and effective.**

In the short term, Health Canada’s activities are expected to result in increased safety and effectiveness (i.e., efficacy) of biologics on the Canadian market. Overall, while Health Canada has in place processes and authorities that are intended to contribute to the safety and efficacy of biologic products on the market, there are also a number of gaps that, if addressed, would further contribute to this objective.

#### Pre-market stage

At the pre-market stage, the information requirements for pre-market reviews are complex and detailed. External key informants generally agreed that Health Canada considers the appropriate type and quality of information in pre-market review, although some would like to see Health Canada incorporate more foreign data, including foreign approvals, into the review process.

Almost all respondents to the biologics industry surveys agreed that Health Canada’s pre-market reviews are rigorous, and that Health Canada has adequate pre-market processes in place to ensure the quality and the efficacy of these products, as well as processes to help ensure an adequate level of product safety.
On the other hand, since many products are not tested on the population for whom they are intended, the data included in a drug submission do not always reflect the full safety or efficacy profile of the product (paediatric populations are a case in point). Furthermore, some US and Canadian studies have found a link, though not a causal relationship, between the speed of the approval process and subsequent post-market safety issues.\(^\text{58}\) An important empirical question for regulatory agencies, therefore, is whether faster approval times result in more unsafe products reaching the market.

More generally, the existence of a rigorous review process does not necessarily support the conclusion that, over time, safer and more effective drugs are being made available on the Canadian market, or that the overall safety and effectiveness of drugs on the market has improved.

**Post-market stage**

The available data show that between 2005 and August 2012, 19% of the recall notices relating to biologics were Type I – issued when there is reasonable probability that use of or exposure to the product will cause serious adverse health consequences or death. See Appendix C for more detailed information.

At the post-market stage, Health Canada, along with other regulators, has recognized the need to enhance post-market surveillance in order to better protect patient health and safety. As described in Section 5.4.5, progress has been made in some areas. Most recently, Bill C-17 proposed amendments to the *Food and Drugs Act* that would give Health Canada the authority to require persons to provide information within their control for the purpose of assessing serious risks to health, and to require manufacturers to compile information, conduct new tests or studies, and/or monitor experience, for the purpose of obtaining additional information. Bill C-17 also proposed amendments that would require health care institutions to report adverse drug reactions.

---

\(^{58}\) In the US, Olson (2002) found that a one-month reduction in a pharmaceutical drug’s approval time through the FDA is associated with a 1% increase in expected reports of adverse drug reaction hospitalizations and a 2% increase in expected reports of adverse drug reaction deaths (p. 27). In Canada, Lexchin (2012) found that 23.7% (84 out of 434) of the new active substances (NASs) approved by Health Canada between January 1, 1995, and December 31, 2010, had safety issues, defined as having been withdrawn from the market and/or receiving a serious safety warning. This included 68 products with serious safety warnings; 9 with serious safety warnings which were then withdrawn from the market; and 7 that were withdrawn without previous safety warnings. The study estimated that NASs receiving a standard review had a probability of 19.8% of experiencing a safety issue, versus a probability of 34.2% for NASs receiving a priority review. For those NASs that were not major therapeutic advances (n=81), the probability of experiencing a safety issue was 36.0% (Lexchin, 2012, p. E1). While the study included both pharmaceutical and biologic drug submissions, the results were not disaggregated by product line.
In the area of compliance and enforcement, Bill C-17 includes a provision that would give Health Canada the authority to recall unsafe therapeutic products, as well as provisions for increased penalties for non-compliance. If implemented, these provisions may address concerns expressed by some external key informants about what they perceive as the relatively few enforcement options available to Health Canada to address noncompliance issues. External key informants also raised concerns about the extent to which Health Canada monitors compliance with NOC/cs. The evaluation could not determine the extent to which such monitoring occurs.

Among industry survey respondents, a majority of respondents to the biologics industry survey believe that Health Canada’s post-market surveillance and monitoring activities, as well as its compliance and enforcement activities, effectively support an adequate level of biologic safety and quality in Canada.

6.4 Industry compliance

The available data suggests that serious industry non-compliance is relatively uncommon. There are opportunities to improve compliance reporting by focusing to a greater extent on outcomes and disaggregating compliance reporting by product line.

In the short term, Health Canada’s activities are expected to lead to increased industry compliance with regulatory requirements relating to biologics. Overall, while the available information suggests a high level of industry compliance, a variety of data limitations, including inconsistencies in reporting over time, inability to extrapolate compliance rates to the regulated industry as a whole, reporting that is aggregated across several product lines, and minimal information on the nature, seriousness, frequency, or prevalence of non-compliances, hamper a more detailed understanding.

The following information is available on industry compliance:

- **Clinical trial compliance.** Compliance among inspected clinical trial sites is high. According to a summary report of inspections conducted between April 2004 and March 2011, 92% of inspected sites received a compliant rating (Inspectorate, 2012e). The majority of the observations noted during these inspections pertained to deficiencies in quality systems and procedures (primarily GCP and records). Of the observations, 54% were considered minor, 39% were considered major, and 1% were considered critical. Given that only 2% of sites are targeted for inspection, this compliance rate cannot be generalized to the entire clinical trial industry. Furthermore, since GCP inspection and compliance data is not tracked by product category (biologic or pharmaceutical drug), it is not possible to separately analyse GCP compliance within these two product lines.

- **GMP compliance.** There is a high level of compliance with GMP among domestic drug establishments. Over the eight-year period between 2005–2006 and 2012–2013, GMP compliance among inspected establishments ranged between 95% and 98%. Like clinical trial inspection data, GMP inspection data is not disaggregated by product category, but includes domestic GMP inspections for biologics and pharmaceutical drugs, as well as veterinary drugs. Therefore, it is not possible to separately analyse GMP compliance within the biologics
and pharmaceutical drugs industries. As previously noted, the FDA reports GMP compliance data by product category.\textsuperscript{59}

- **Inspections of blood, CTO, and semen establishments.** In most years for which data are available, inspections have found 100% compliance among inspected blood, CTO, and donor semen establishments.
  
  - Between 2005–2006 and 2012–2013, there was 100% compliance among inspected blood establishments.
  
  - In 2009–2010 and 2012–2013, there was 100% compliance among inspected CTO establishments, while in the two intervening years, the compliance rate was 88%.\textsuperscript{60}
  
  - Between 2005–2006 and 2012–2013, compliance among inspected donor semen establishments has ranged between 100% and 89%.

- **Compliance with post-market reporting requirements.** Between 2004–2005 and 2012–2013, the PMRC (now GVP) inspection program found 100% compliance with post-market reporting requirements among inspected biologics and pharmaceutical drug establishments. As with GMP and GCP compliance data, these data are not disaggregated by product type.

- **Compliance of imported products.** National Border Integrity Program data show that relatively few shipments of biologics and radiopharmaceuticals (Schedules C and D) were inspected between 2010–2011 and 2012–2013 (n=159), and most (88%) were released. The remaining 12% of shipments were refused entry at the border for noncompliance with Canadian regulations. There were no instances of counterfeit product among the shipments refused.

See Appendix C for more detailed information on industry compliance.

The available data seem to suggest that serious non-compliance is relatively uncommon. Over the period of the evaluation, however, Health Canada has not reported regularly or consistently on the nature, seriousness, frequency, or prevalence of non-compliances related to biologics, and has focused its reporting, instead, on quantifying activities and outputs. Furthermore, some of Health Canada’s reporting on compliance, including GMP, GCP, and GVP data, is aggregated across multiple product categories, including pharmaceutical, biologic and veterinary drugs.

The Inspectorate has recently developed an annual inspection summary report that will be published on the Health Canada website. The 2012–2013 report includes a description of Inspectorate activities and outputs, describes the overall compliance rate of industry, describes the risk ratings of observations noted during inspections, and gives examples of the common observations cited in non-compliant establishments (Health Canada, 2013j). According to the

\textsuperscript{59} Recent events have focused attention on Health Canada’s GMP inspection program. While pharmaceuticals have been implicated in several cases, quality issues have also surfaced in relation to biologics. For example, Sanofi Pasteur recalled about 4,700 vials (47,000) doses of a tuberculosis vaccine, also used in treating bladder cancer under the trade name ImmuCyst, after routine inspections in May and June 2012 raised concerns about mould contamination at the company’s Toronto facility (Branswell, 2012; Canadian Press, 2013). As noted, however, without aggregate reporting on GMP compliance by product category, it is not possible to assess overall compliance levels within the biologics industry specifically.

\textsuperscript{60} The CTO Regulations came into force in December 2007 except one section of the Regulations, which came into force in June 2008. There were no inspections in 2007–2008 and 2008–2009.
report, Health Canada conducted 1,387 inspections in 2012–2013 across all of its inspection programs (covering human drugs, medical devices, natural health products, blood, donor semen, and CTO), made hundreds of observations requiring corrective actions, and issued 33 non-compliant ratings. The report does not contain any information on actions taken by the Inspectorate in response to non-compliance, nor does it report GMP, GCP and GVP compliance information separately for pharmaceutical and biologic drugs. However, inspection and compliance information for semen, blood and CTO are reported by product category.

Inspectorate representatives identified a number of challenges to disaggregating compliance reporting, particularly for the GMP and GVP inspection programs. They noted that while the pre-market function of the BP is aligned around the product, this is not necessarily true of the compliance function, which is oriented around processes. Thus, a GMP inspection of a manufacturing facility that produces both pharmaceuticals and biologics focuses on the overall manufacturing process, not on the products manufactured there, and the inspection outcome is applicable to the facility as a whole. The Inspectorate estimates that of 1,763 GMP inspections conducted between 2009–2010 and 2012–2013, 3% were of facilities involved only with biologics, while the same proportion of inspections were of facilities involved only with radiopharmaceuticals. The majority (81%) were of facilities involved only with pharmaceuticals. The remaining inspections were of facilities involved with various combinations of biologics, radiopharmaceuticals, and pharmaceuticals.

Inspectorate representatives noted, however, that similar constraints do not present themselves with respect to GCP inspections. Clinical trials involve a single product, which is either a pharmaceutical or a biologic, and therefore clinical trial inspection data could more easily be reported by product type. The Inspectorate estimates that between 2009–2010 and 2012–2013, approximately 15% of completed GCP inspections involved biologics, while the remainder involved pharmaceutical drugs.

Inspectorate representatives also identified technical difficulties in extracting the necessary information out of the Inspectorate’s inspection database (the Inspection Reporting System) due to the structure of the relevant data fields. Given these challenges, they questioned the utility of reporting inspection and compliance data separately by product line. That said, they acknowledged that in the context of Health Canada’s current PAA, in which the Pharmaceuticals Program and the Biologics Program are distinct program areas, there is a need to report program-specific inspection and compliance data.61

6.5 Adoption of safe behaviours

The extent to which Health Canada activities have led stakeholders to adopt safe behaviours is unknown. Health Canada’s ongoing evaluation of the effectiveness of its risk communications may shed light on this question.

---

61 Although the focus of this discussion is inspection and compliance data, the point also applies to financial reporting for the Inspectorate’s activities.
In the intermediate term, HPFB’s activities are expected to lead external stakeholders to adopt safe behaviours associated with biologics. The extent to which this has occurred could not be determined by the evaluation.

To date, Health Canada has not evaluated the impact of its activities on stakeholder behaviour, although, as previously mentioned, it will conclude an Evaluation of the Effectiveness of Risk Communications in March 2014. The survey of stakeholders was intended to provide evidence to support conclusions on this outcome, but achieved a low response rate and could not fulfill this role in practice.

The literature review found some evidence of potentially unsafe behaviours and/or practices associated with the use of drugs. One recent study estimated that 11% of drugs prescribed in primary practice were prescribed for an off-label indication; in 79% of these cases, there was no strong scientific evidence of the efficacy of the products concerned with respect to their intended uses (Eguale et al., 2012). However, it is important to note off-label use is not inherently unsafe; indeed, physicians have the authority to prescribe off-label under the Practice of Medicine.

While Health Canada currently does not have jurisdiction to regulate use, it can influence use indirectly through other channels, such as product labelling and the preparation and dissemination of knowledge products and risk communications. The Branch is also responsible for product reviews, and has the ability to refuse market authorization to products that are unsafe.

6.6 Use of scientific evidence and risk-benefit analysis

The use of scientific evidence and risk-benefit analysis (and/or risk-based analysis) is formally incorporated into Health Canada’s pre-market and post-market processes.

In the intermediate term, the BP envisions an increase in the use of scientific evidence and risk-benefit analysis to inform Health Canada decision making. Health Canada has integrated the use of scientific evidence and risk-benefit analysis into its decision-making processes and activities, although the evaluation could not determine whether their use has increased over the period of the evaluation.

The use of scientific evidence and risk-benefit analysis is formally integrated into Health Canada’s decision-making process. The Health Canada Decision-Making Framework for Identifying, Assessing and Managing Health Risks sets out an approach to decision making in which risk analysis and management activities are central (Health Canada, 2000). The framework is used to guide the BP decision-making process, although the evaluation could not assess the consistency with which it is applied in practice.
The use of scientific evidence and risk-benefit analysis\(^\text{62}\) (and/or risk-based analysis) is also formally incorporated into Health Canada’s pre-market and post-market processes. Some examples are given below (note that this is not intended to be an exhaustive list).

- The information requirements for biologics submissions are complex and detailed. Scientific evidence is required to demonstrate a product’s safety, efficacy and quality, while Health Canada decisions to grant market authorization are based on a benefit/risk assessment.

- Due to the greater difficulties in consistently manufacturing biologic (Schedule D) drugs, these products are subject to the additional requirements of the LRP. At the post-market stage, manufacturers of biologic drugs are required to submit YBPR to Health Canada.

- MHPD has recently developed and implemented a standardized approach to post-market activities for all of the product lines regulated by HPFB. Standardized processes are in place for signal detection, assessment, and risk management, which incorporate consideration of scientific evidence and risk-benefit analysis.

- The Inspectorate’s recently-developed Compliance and Enforcement Risk Evaluation Guide sets out a structured approach to evaluating and managing health risks through its compliance and enforcement activities (Inspectorate, 2012c).

- The Inspectorate’s inspection programs for CTO, blood, and semen, as well as its GMP and GCP programs, are risk-based, and are intended to allow the Inspectorate to focus its resources on areas of high risk.

In addition to incorporating scientific evidence and risk-benefit/risk-based analysis into its processes, Health Canada has established a number of expert committees and panels to provide guidance on regulatory and policy development in various areas. Health Canada has used some of their recommendations to guide policy and regulatory development. A few examples are briefly described below; for a more complete list, please see Appendix C.

- The Expert Advisory Committee on the Vigilance of Health Products (EAC-VHP) was established in 2006 to provide HPFB with ongoing expert strategic policy advice on the safety and effectiveness of marketed health products for human use. Since its inception in 2006, the Committee has advised HPFB on risk communications, consumer reporting to the Canada Vigilance Program, signal detection and assessment, benefit-risk assessment, tracking of adverse reactions related to off-label use, and enhancing post-market surveillance through collaboration with provincial systems and researchers through the DSEN. MHPD used the Committee’s advice in developing the Recommendations for the Appropriate Use of Cough and Cold Products in Children document.

- The Paediatric Expert Advisory Committee (PEAC) was established in 2009 to provide HPFB with expert advice and public involvement in the development, licensing, and post-market surveillance of health products destined for children and pregnant and nursing mothers. The PEAC’s examination of off-label drug use in the paediatric population led to a “Mind the

---

\(^{62}\) Although the evaluation framework developed by Health Canada refers to “risk-benefit analysis,” many Health Canada documents refer to risk analysis, risk-based analysis, and risk-based approaches. These are distinct concepts, but the discussion here treats them as largely similar.
Gap” study initiated by the Office of Paediatric Initiatives to address issues related to off-label drug use in children.

- The EAC on Cells, Tissues and Organs advises BGTD on issues related to the safety, quality and efficacy of CTO intended for use as transplants. The EAC provided recommendations for amendments to the CTO Regulations in 2009, gave input into the guidance document for CTO establishments, and advised on development of a CTO surveillance framework.

- The EAC on Blood Regulation advises BGTD on issues of risk management in the national blood system. Among other things, the EAP has provided opinions and advice to BGTD based on PHAC’s surveillance reports for HIV and AIDS in Canada, provided advice on the development of CTO surveillance, and investigated safety procedures around specific blood products.

- Several committees have advised Health Canada regarding specific products, and their advice has informed Health Canada’s decision making regarding these products. For example:
  - based on recommendations of the EAP on Avastin, Health Canada suspended the NOC/c for Avastin in combination with paclitaxel for treatment of patients with metastatic breast cancer; and
  - recommendations from the EAP on Prochymal were included as conditions for the manufacturer to meet as part of the NOC/c for this product.

A variety of other committees have been established — some fairly recently — to address metabolic and endocrine therapies, oncology therapies, pharmaceutical sciences and clinical pharmacology, and bioequivalence of gender-specific drug products, and have been active to varying degrees. Several committees, addressing human reproductive technologies, modified-release dosage forms, and the SAP, have completed their mandates, and two (advising on musculoskeletal therapies and neurological therapies) have been cancelled.

From an evaluation perspective, it is unclear how an increase in the use of scientific evidence and risk-benefit/risk-based analysis could be meaningfully achieved or measured. Instead, it may be more reasonable to expect Health Canada to use scientific evidence and risk-benefit/risk-based analysis consistently to inform decision making.

### 6.7 Timely regulatory response to risks

Recognizing that policy and regulatory development is often a lengthy process, there are instances in which Health Canada’s response has taken longer than expected to implement. The overall timeliness of the biologics signal process (i.e., from signal detection to ultimate action taken by Health Canada) could not be determined.

A timely regulatory response to identified risks is expected to result from BP activities in the intermediate term. Arriving at a broad conclusion on this outcome is complicated by the variety of ways in which it may be measured and by challenges in determining when to consider risks to have first been identified by Health Canada.
**Timeliness with which Health Canada develops regulatory/policy responses**

One way of measuring this outcome is to examine the timeliness with which Health Canada develops regulatory and policy responses to identified risks. Often it is difficult to know when Health Canada first identified a specific risk. Moreover, while it is well-known that regulatory (if not policy) development is typically a lengthy process, there are no objective standards against which the timeliness of Health Canada’s response can be assessed.⁶³

Table 8 below identifies regulatory projects led by the Biologics Program between 1999 and 2013, including the date the regulatory projects were initiated and the date the regulations were published in Canada Gazette II (CG II).⁶⁴

<table>
<thead>
<tr>
<th>Regulatory project</th>
<th>Date initiated</th>
<th>Date published in CGII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Plasma collected by Plasmapheresis</td>
<td>2001</td>
<td>2006</td>
</tr>
<tr>
<td>Amendments to Part C, Division 4 for Smallpox Vaccine</td>
<td>2005</td>
<td>2006</td>
</tr>
<tr>
<td>Regulations for PERs for Basic Research</td>
<td>2006</td>
<td>2012</td>
</tr>
<tr>
<td>Extraordinary Use New Drugs</td>
<td>2006</td>
<td>2011</td>
</tr>
<tr>
<td>CTO Regulations</td>
<td>mid-1990s</td>
<td>2007 (Phase I)</td>
</tr>
<tr>
<td>Blood Regulations</td>
<td>1997</td>
<td>Expected 2014</td>
</tr>
</tbody>
</table>

Note: The date initiated refers to the start of the policy work, not the regulatory drafting. For the CTO and Blood Regulations, the date initiated was estimated. Work in both areas was accomplished in stages as described in Section 5.4.1.

There are two instances in which Health Canada’s response to acknowledged risks has taken longer than expected to implement. These are the development and implementation of the Blood Regulations and the development and implementation of the CTO Regulations.

Health Canada acknowledged the risks associated with the blood supply in 1993 with the launch of the Krever Inquiry, and work on a new regulatory framework for blood began following the Krever Report in 1997, using a standards-based approach. Several delays were encountered, and re-publication of the proposed regulations took place in 2012. The regulations are expected to come into force in the fall of 2014.

---

⁶³ There are three main stages involved in the process of developing regulations in Canada: preliminary research and decision to regulate; pre-publication of a proposed regulation; and final approval, publication, and registration of the proposed regulation. While Stages Two and Three combined typically require between 6 to 24 months to complete, there are no timelines associated with the preliminary research stage. It is also important to note that the time to bring regulations to CGII includes non-program time, such as time spent awaiting ministerial approval or legal review, or time spent in the actual drafting of the regulations.

⁶⁴ During this time, BP staff also worked on other Branch-level regulations.
In the case of the CTO Regulations, the risks associated with CTO were first identified in the mid-1990s, when an external report on the safety of human organ and tissue transplantation in Canada recommended that national standards for organs and tissue transplantation be established; that a process be developed for the mandatory certification and accreditation of all transplant programs; and that these programs be accredited and inspected by a national agency (GoC, 2007). Phase I of the CTO regulatory framework was implemented in June 2007 (GoC, 2007), and Phase II is still in development.

In both cases, BGTD took a standards-based approach to regulatory development, i.e., the regulations were developed by using standards created by Standards Development Organizations, rather than by the regulatory authority (BGTD) itself. A 2009 audit of BGTD’s management and implementation of the standards-based approach noted that “both of these projects took far more time and resources to complete than originally planned,” although it also acknowledged that “past experiences within the Department in developing regulations have also shown lengthy development times” (AAB, 2009, p. 6). The audit noted that if it becomes clear that future regulatory projects will take several years to complete, Health Canada should “ensure that adequate measures are in place to mitigate any risks to health and safety in the interim” (AAB, 2009, p. 6).

Delays in Health Canada’s response may be due to the complexity of the regulations and changing priorities over time, although as the discussion above has indicated, other factors may also have contributed. With respect to the latter point, it is important to note that in some cases, despite having identified risks and developed a regulatory response to those risks, Health Canada has been unable to proceed with fully implementing some of its planned initiatives due to the failure of enabling legislation to be passed into law. Several planned initiatives were affected by the fact that Bill C-51 did not become law, including the implementation of a progressive licensing framework, mandatory adverse reaction reporting for health care institutions, and new administration and enforcement measures, including the power to order mandatory recalls, among others. Similar provisions have recently been re-introduced with Bill C-17.

**Timeliness of response to post-market safety issues**

Another way of assessing the timeliness of Health Canada’s response to identified risks is to examine the timeliness of its response to post-market safety issues. Health Canada’s Departmental Performance Reports for 2011–2012 reports that 93% of post-market signal assessments for pharmaceuticals, medical devices, biologics, and natural health products were completed within service standards in that fiscal year (Health Canada, 2012a). A detailed breakdown by product category was not provided.

The OAG examined the timeliness of Health Canada’s response to safety signals for pharmaceutical drugs in its 2011 report. While the scope of the OAG’s audit was limited to pharmaceutical drugs, the OAG’s broader observations are relevant to biologics, since as noted above, MHPD has developed a standardized process for signal detection and assessment. In

---

65 BP representatives noted that approximately 50% of the time required for the CTO regulations from 2004 on was time awaiting legal review of instructions or time spent by the Drafting Unit on the actual regulatory drafting, which the BP itself had no control over.

66 BP representatives noted that an Interim Policy on CTO safety was drafted and implemented in 2003.
particular, the OAG noted that while 34 of the 54 safety assessments it examined as part of the audit were completed within the established timelines, the Department’s approach to measuring its performance does not consider the amount of time a potential safety issue may wait before an assessment begins; the amount of time an assessment may be placed on hold; the amount of time needed to obtain additional information from external parties; and the total number of calendar days, instead of working days, taken to complete the assessment (OAG, 2011, p. 24). The OAG noted that when these factors were considered, Health Canada took at least one year to complete 34 of its 54 assessments, and in some cases took significantly longer — two or three years (OAG, 2011, p. 24). The OAG concluded that the Department’s “assessment of, and response to, potential safety issues is not timely” (OAG, 2011, p. 22).

Since the OAG’s analysis was specific to pharmaceutical drugs, the evaluation undertook a detailed analysis of Health Canada’s response to safety signals for biologics using administrative data provided by MHPD. Detailed data are provided in Appendix C. The analysis showed the following:

- Biologics signals waited, on average, 14 days to be assigned for signal assessment.
- MHPD introduced unofficial performance standards for signal assessments in April 2007. In the case of biologics, 92% of signal assessments assigned between November 2008 and October 2012 were completed within 130 working days. 67 Biologics signal assessments completed in this period had a median processing time of 46 days.

While it is important for Health Canada to complete signal assessments in a timely fashion, it is also important, from a safety perspective, that it implement the recommended actions stemming from completed assessments in a timely fashion. Due to a limited number of cases for which complete data were available, the evaluation was unable to examine the overall timeliness of the biologics signal process (i.e., to examine the total time elapsed from signal detection to ultimate action taken by Health Canada). 68 Further objectivity of the analysis could be obtained by comparing Health Canada’s response against that of its international counterparts.

---

67 A pre- and post-April 2007 comparison could not be performed for biologics, since all biologics signal assessments with an assigned date recorded were assigned after April 2007, specifically between November 2008 and October 2012.

68 However, such an analysis, focusing specifically on recommendations for risk communications, was completed as part of the HDP evaluation. The HDP evaluation examined a subset of completed pharmaceutical drugs signal assessments that produced a recommendation for a risk communication. The evaluation examined all pharmaceutical drugs signal assessments completed in 2010, 2011, and 2012 that produced a recommendation for a risk communication (n=38). The evaluation originally planned to analyse whether, and the timeliness with which, the recommendations stemming from all completed pharmaceutical and biologic drug signal assessments were implemented by Health Canada. However, the data necessary to complete this analysis were unavailable, as internal Health Canada resources would have been required to compile it from a variety of sources. The evaluation therefore restricted its analysis to signal assessments completed in 2010, 2011, and 2012 that recommended the issuance of a risk communication, since the information necessary to support this analysis could be compiled from public sources (i.e., the MedEffect website). The results of the analysis are reported in the HDP evaluation. A similar analysis could not be undertaken for biologics due to a limited number of completed signal assessments in this time period (n=6) that produced a recommendation for a risk communication. Furthermore, all necessary data points to complete the analysis were available in only three of these six cases.
At present, the data necessary to complete any detailed analysis of Health Canada’s post-market activities is highly dispersed and inconsistently maintained. Given Health Canada’s stated intention to enhance post-market surveillance, a more comprehensive, consistent, and centralized approach to data collection and information management for its post-market surveillance activities seems warranted. While a database solution would be ideal, improvements could also be made through relatively straightforward and low-cost adjustments to the current Excel-based system. Examples include standardizing data entry through the use of predefined codes, assigning unique identifiers to files at the signal detection stage, and using these unique identifiers through all stages of the signal process, in order to enable linking of records across spreadsheets.

### 6.8 International harmonization

**Health Canada is actively engaged in a variety of international fora. Health Canada is viewed by international key informants as a constructive participant in bilateral and multilateral engagement.**

In the intermediate term, BP activities are expected to produce increased international harmonization of regulatory requirements for biologics. Harmonization is defined as “the development, adoption, and implementation of international technical standards for the development, registration, and control of pharmaceuticals and medical devices,” as well as “the convergence of regulatory practices and processes” (TPD, 2004, p. 9).

In this area, Health Canada has focused on developing and strengthening regulatory cooperation and work-sharing activities with key international counterparts; being actively involved in harmonization of international standards/technical requirements and in regulatory convergence initiatives; and strategically engaging with countries whose regulatory systems are in development, in order to build capacity. The evaluation found evidence that the BP has been working toward greater international harmonization and has made progress in some areas.

- Health Canada is an official observer to and active participant in the ICH, which was established by the regulatory authorities and pharmaceutical industries of Europe, Japan, and the US to harmonize technical requirements and ensure the safety, quality, and efficacy of human pharmaceuticals (HPFB, 2012b, p. 9). In this capacity, Health Canada participates in the development and revision of ICH guidance and standards, as well as a variety of committees and working groups, and chairs a special task force to examine the development of a strategic plan for ICH training. Health Canada also participates in the development of an electronic submission standard (eCTD) (HPFB, 2012b, p. 9). Health Canada has adopted 40 ICH guidelines for biologics.

- HPFB has MRAs on GMP compliance with the European Community, Switzerland, Iceland, Liechtenstein, Norway, and Australia.
• Health Canada is a member of the Pharmaceutical Inspection Cooperation Scheme (PIC/S), an organization comprised of 44 regulatory authorities. As a PIC/S member, Health Canada shares inspection reports with other members and participates in various inspection-related activities.

• HPFB has formal information-sharing agreements with the FDA, Australia’s Therapeutic Goods Administration (TGA), and the European Community.

• Health Canada and the FDA participate in the RCC, the overall objective of which is to better align the two countries’ regulatory approaches. Initiatives are underway in relation to developing a common gateway for electronic submissions and GMPs.

• BGTD and the FDA’s Center for Biologics Evaluation and Research (CBER) have recently launched a collaborative initiative, the objectives of which are more frequent bilateral engagement between the two organizations on common regulatory and policy issues, work-sharing in areas of mutual interest, and resource sharing related to international meetings (HPFB, 2012b, p. 37).

• HPFB is involved in an Embedded Experts Initiative with the EMA, whereby an HPFB staff person is embedded within the EMA to work on joint projects. Proposed activities include observing monthly Pharmacovigilance Risk Assessment Committee meetings, implementing strategies for evolving ICH pharmacovigilance guidelines, harmonizing approaches to benefit-risk evaluation assessment standards and methodologies, and developing effective risk minimization and communication strategies. HPFB also participates in meetings of various other EMA working parties and groups related to pharmacovigilance, quality, and GCP inspections (HPFB, 2012b, pp. 33–35).

• Health Canada participates in a number of initiatives of the World Health Organization (WHO). It contributes to the WHO’s Prequalification of Medicines Program and International Drug Monitoring Program, and participates in the Council for International Organizations of Medical Sciences. BGTD serves as a prequalification authority for the WHO’s Vaccine Prequalification Program and was also invited to be a founding member of the WHO’s Blood Regulators Network. BGTD helped to develop the WHO’s GMP for Blood Establishments, contributed to the WHO’s guidance document on follow-on biosimilars, participates in the development of international physical reference standards and written guidance for WHO collaborating centres, and was recently confirmed as a WHO Laboratory Collaborating Centre for Biologics.

• Other international fora in which Health Canada participates include the Asia-Pacific Economic Cooperation, the Heads of Agencies Consortium, the International Laboratory Forum on Counterfeit Medicines, the International Generic Drug Regulators’ Group, the Official Medicines Control Laboratories Network, the Pan American Health Organization, the Pan American Network for Drug Regulatory Harmonization Cooperation, and many others.

All international key informants regard Health Canada as a constructive participant in bilateral and multilateral engagement, describing Health Canada as consistent, reliable, strategic, creative, well-informed, like-minded, cooperative, and constructive. Several pointed out that Health Canada is perceived as a more neutral and thoughtful participant in international fora than some of the larger players. Nonetheless, international key informants noted that Health Canada, like other regulators, may face a variety of obstacles to increased harmonization and further...
international collaboration, including limited resources to contribute to international activities; political or economic considerations taking priority; legislative constraints to harmonization (i.e., lack of a legislative basis for harmonized processes); increasingly prescriptive and detailed national legislation; and philosophical differences (perceived as existing primarily between the US approach and the rest of the world).

6.9 Long-term outcomes

Health Canada’s activities have likely contributed to a reduced exposure to health risks and fewer adverse reactions.

In the long term, BP activities are expected to contribute to reduced health risks and adverse events associated with the use of biologics, as well as increased public confidence in these products and the related regulatory systems. BP activities likely have an impact in these areas, although many other factors may also influence these outcomes.

Program activities such as approval of safe biologics whose benefits outweigh risk risks, post-market surveillance and monitoring, and compliance and enforcement of the regulatory frameworks should contribute to reduced health risks and adverse events associated with the use of these products. For example, removing unsafe products from the market through recalls and preventing non-compliant products from entering Canada likely avert adverse health effects in humans that would have occurred had these actions not been taken.

While these and other program activities have certainly contributed to reducing health risks and adverse events associated with the use of biologics, finding concrete evidence of these outcomes is challenging. The available indicators lend themselves to a variety of interpretations. For example, the number of adverse reaction reports submitted to the Canada Vigilance Program has been increasing steadily over time. However, this is likely due to the greater number and variety of products on the market along with increased recognition of the need or obligation to report adverse reactions, and not necessarily to an increase in unsafe products per se. Indeed, the proportion of adverse reaction reports that are classified as “serious” — i.e., that involve congenital anomaly, death, disability, hospitalization, another medically important condition, or that are life-threatening (Health Canada, 2012g) — has remained stable since 2001, accounting for just over two thirds of all reports submitted each year (MHPD, 2012a).

With respect to public confidence, survey data show a high level of confidence among consumers in the safety of drugs and the regulatory system. In 2003 and 2006, 84% and 86%, respectively, of consumers were confident in the safety of prescription drugs (Decima Research, 2003, 2006). However, the proportion expressing confidence declined slightly in 2010, when 65% of Canadians reported feeling that the medications approved by Health Canada are safe (Nanos Research, 2010). These surveys did not, however, distinguish between pharmaceutical and biologic drugs. Some limited information is available from a 2007 survey, which showed that most Canadians were either somewhat concerned (29%) or concerned (48%) about the safety of medicines (both pharmaceuticals and biologics), while slightly fewer were somewhat concerned (25%) or concerned (43%) about the safety of vaccines (Nanos Research, 2007).
Most consumers also expressed confidence in the regulatory system. In 2003, 85% of consumers expressed confidence in the systems and safeguards in place to ensure the safety of prescription drugs for sale in Canada (Decima Research, 2003). In 2006, about 78% of respondents expressed confidence in how the federal government monitors and regulates drug safety and effectiveness (Decima Research, 2006). Again, these findings relate to all drugs, not biologics specifically.

Ultimately, Health Canada hopes to achieve a sustainable, cost-efficient, responsive, and science-based regulatory system for biologics in Canada. The evaluation found that Health Canada uses scientific evidence and consults with stakeholders in policy and regulatory development. While recent updates to user fees for biologics help to support the sustainability of the regulatory system for biologic drugs, BP representatives noted that the fees did not consider the greater complexity of biologics submissions or the extra costs associated with OSEs and the LRP. Furthermore, other product lines such as CTO and blood products are not cost-recovered.

### 6.10 Unintended consequences

External key informants identified a number of unintended consequences stemming from Health Canada’s approach to regulating biologics. For the most part, these related to the increased burden and cost associated with complying with regulatory requirements. It was also suggested that in some cases, this may ultimately have a negative effect on research, product development and/or some areas of medicine, and access to health products. The following examples were given:

- Current regulations governing clinical trials may result in declining research activity in academic settings relative to industry, since only larger pharmaceutical and biotechnology companies are likely to have the resources necessary to comply with the regulations.
- In a related vein, current regulation in the radiopharmaceutical sector may have a detrimental effect on nuclear medicine in Canada by driving up the costs of regulatory compliance; this could lead to a loss and/or slowdown of research in Canada relative to other jurisdictions, the transition of isotope research to large pharmaceutical companies (who were viewed as the only organizations with the resources to fund such research), and reduced access to new products.
- As existing drugs developed for a new indication are sometimes not eligible for data protection in Canada, some of these products are not being marketed in the country.
- Requiring manufacturers of blood bags with new anticoagulants or additive solutions to be certified and have a DIN resulted in some firms leaving the market on the grounds that it was too costly to continue production.

The evaluation could not assess the extent to which these unintended consequences have, in fact, occurred.

---

69 The surveys were also identified early in the evaluation planning stages as potential data sources regarding unintended consequences. Ultimately, the surveys did not include questions relating to unintended consequences, due to length considerations.
7.0 Findings – efficiency and economy

Program performance and financial information was insufficient to properly demonstrate efficiency and economy. HPFB has recently implemented a number of improvements to its approach to financial reporting, which should facilitate future analysis.

The Treasury Board Policy on Evaluation (2009) and guidance document, Assessing Program Resource Utilization When Evaluating Federal Programs (2013), defines the demonstration of economy and efficiency as an assessment of resource utilization in relation to the production of outputs and progress toward expected outcomes. This assessment is based on the assumption that departments have standardized performance measurement systems and that financial systems link information about program costs to specific inputs, activities, outputs and expected results.

The data structure and level of financial and human resource information provided for the program did not facilitate the assessment of whether program outputs were produced efficiently, or whether expected outcomes were produced economically. Specifically, the lack of output/outcome-specific costing data limited the ability to use cost-comparative approaches. In terms of assessing economy, challenges in tracking funding within the broader program envelope limited the assessment.

For fiscal year 2007–2008 and earlier, financial reporting was based on Health Canada’s former PAA. Under this PAA, biologics activities fell under the Health Products and Food Program Activity. Program sub-Activities were as follows:

- pre-market regulatory evaluation and process improvement
- information, education, and outreach on health products, food, and nutrition
- monitoring safety and therapeutic effectiveness and risk management
- transparency, public accountability, and stakeholder relationships.

Financial reporting was linked to these four Program sub-Activities and to sub-sub-Activities representing, at a more detailed level, the functional activities carried out by Health Canada personnel as part of the sub-Activities. However, it is not possible to link this information to what, since 2008–09, has been considered the BP.

In 2007–08, Health Canada’s PAA was restructured. Under this version of the PAA, the relevant Program Activity is Health Products, and the Program sub-Activities are as follows:

- Pharmaceutical Human Drugs
- Biologics and Radiopharmaceuticals
- Medical Devices
- Veterinary Drugs.\(^{70}\)

---

\(^{70}\) Further restructuring of the PAA in 2012 resulted in the creation of a larger Pharmaceutical Drugs Program by combining the Pharmaceutical Human Drugs Program and the Veterinary Drugs Program.
From 2008–2009 through 2011–2012, financial reporting was linked to the four Program sub-Activities listed above. Table 9 presents the available data on BP expenditures for 2009–2010 to 2011–2012, with and without revenues. It is important to note that the available expenditure data do not include overhead, which is not coded at the sub-Program level but only at the Program level (i.e., Health Products). As a result, the available financial information does not provide an accurate depiction of total Program expenditures.
### Table 9: Total expenditures ($), BP, 2009–2010 to 2011–2012

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>w/o revenue</td>
<td>w/ revenue</td>
<td>Revenue</td>
</tr>
<tr>
<td>Biologics and Genetic Therapies</td>
<td>34,482,021</td>
<td>30,976,803</td>
<td>-3,505,218</td>
</tr>
<tr>
<td>Therapeutic Products</td>
<td>493,501</td>
<td>493,501</td>
<td>0</td>
</tr>
<tr>
<td>Inspectorate</td>
<td>639,717</td>
<td>558,324</td>
<td>0</td>
</tr>
<tr>
<td>Marketed Health Products</td>
<td>3,458,166</td>
<td>3,458,166</td>
<td>0</td>
</tr>
<tr>
<td>Other HPFB Costs</td>
<td>115,819</td>
<td>115,819</td>
<td>0</td>
</tr>
<tr>
<td>HPFB – Regions</td>
<td>108,622</td>
<td>108,622</td>
<td>0</td>
</tr>
<tr>
<td>Total HDP – HPFB</td>
<td>39,297,846</td>
<td>35,711,235</td>
<td>-3,505,218</td>
</tr>
<tr>
<td>RAPB</td>
<td>1,005,115</td>
<td>1,005,115</td>
<td>0</td>
</tr>
<tr>
<td>Total HDP – HPFB and RAPB</td>
<td>40,302,961</td>
<td>36,716,350</td>
<td>-3,505,218</td>
</tr>
</tbody>
</table>

Notes:
1. Figures include Employee Benefit Plans (EPB).
2. Within HPFB, overhead was not coded to sub-program levels prior to 2011–2012. Therefore, sub-program expenditures do not include overhead in 2009–2010 and 2010–2012. In 2011–2012, corporate overhead costs (such as Legal, lease and fit up, etc.) were not yet coded to sub-program levels.
3. HPFB Regions includes British Columbia, Alberta, Nunavut, Northwest Territories, Ontario, Quebec, Atlantic and Manitoba.
4. Other HPFB Costs consists of ADM, Litigation, Office of Consumer and Public Involvement, and PPIAD.
5. RAPB figures do not include Non-controllable, Capital, Grants, or Contributions.
6. Cost recovery revenue was allocated to RAPB starting in 2011–2012.

Sources: HPFB and RAPB.
Similarly, limited information is available on BP budgets. For example, in 2010–2011 and 2011–2012, financial reporting at the Program sub-Activity level did not include budgeted amounts. Instead, budgeted amounts were only reported at the Program level (i.e., Health Products). This, combined with the difficulties in understanding total BP expenditures, makes it impossible to compare budgeted amounts against actual expenditures over time.

Health Canada representatives indicated that HPFB has recently implemented a number of improvements to its approach to financial reporting.

- Although expenditures incurred by overhead organizations such as ADM and PPIAD were not coded consistently to the BP in the past, since 2011–2012, procedures have been put in place to ensure that all expenditures are coded to the appropriate Sub-activity (Biologics, Pharmaceutical Drugs, Medical Devices, etc.) and not at the Program (i.e., Health Products) level.
- Beginning in 2013–2014, notional budgets were revised to ensure proper allocation to the Sub-activity level.
- Beginning in 2014–2015, the federal government will require all expenditure management reporting to be done at the Sub-activity level, or lower, depending on the approved PAA. Health Canada representatives indicated that HPFB is well along the path of being able to plan, budget, and report at this new required level.

In addition to the limitations, described above, of HPFB’s historic approach to reporting on the budgets and expenditures of the BP, a number of other shortcomings in the data also limit their usefulness for analyzing efficiency and economy. For example, while there is information on the number of FTEs allocated to various HPFB directorates and other entities involved in the BP, the number of FTEs allocated to various program activities is unknown.71

A related challenge, from the point of view of assessing efficiency and economy, is that reporting by functional activities, which took place under the previous PAA, has not taken place since 2008–2009. Some examples of functional activities (also referred to as Functional Areas) include screening, product assessment, new submissions, monitoring and surveillance, and education and outreach. Such task- or activity-based reporting is essential to analyzing efficiency and economy because it reflects the time spent by program staff performing various tasks or activities and producing various outputs. As such, this information is important in assessing:

- allocative efficiency, which focuses on the relationship between resources and outcomes;
- operational efficiency, which focuses on the relationship between resources and outputs; and
- economy, which focuses on the optimization (including the minimization) of the use of resources.

In a recent status report on the financial management and performance of the human drugs (including biologics) and medical devices programs under the new cost recovery regime, Health Canada reported that it has introduced financial management controls, including an improved

---

71 According to data provided by HPFB, the number of FTEs allocated to the BP within HPFB increased from 352.16 in 2009–2010 to 449.46 in 2011–2012.
time tracking system, to help validate costing data (Health Canada, 2013n). It is therefore possible that reporting by functional activities has been resumed. In addition, Health Canada reported that it has introduced a variety of other measures to support the efficient delivery of regulatory services, including the following:

- streamlining review processes
- putting systems in place — such as SOPs, guidelines, and training — to support more efficient reviews and applying them consistently to enable improved submission planning
- using foreign review reports and working with other regulatory agencies
- strengthening scientific capacity through hiring and retaining qualified staff
- improving information technology systems to support the submission review process.

In the same report, Health Canada noted that the increased revenue resulting from updated user fees has “allowed activities to be better resourced” and that “cost recovery targets for first decisions met 100% service standards in all program areas”; the same information was also reported in the 2011–2012 DPR. According to BGTD representatives, 100% of first decisions for biologics met the service standards in 2012-2013, a trend that preliminary data suggests will be maintained for 2013-2014.

Based on the analysis completed as part of this evaluation and reported in Section 6.7, the timeliness of submission review for biologics has improved under the new cost recovery framework. In both 2011 and 2012, 100% of NDS and SNDS review cycles for biologics were completed within service standards. This is a substantial improvement over 2010, when 57% and 80% of review cycles for NDS and SNDS, respectively, were completed within target.

These improvements in timeliness do not necessarily mean that submission review is being carried out more efficiently, i.e., it is not necessarily the case that program outputs — in this case, completed reviews — are being produced at lower cost. A more detailed costing analysis, such as the analysis completed in 2007 to support the proposal for updated user fees, which calculated a unit cost for a variety of program activities subject to cost recovery (Health Canada & Spearhead Management Canada Limited, 2007), would shed light on the extent to which efficiencies may have been realized under the new cost recovery regime.

Such an analysis may also help to identify where future updates to the cost recovery framework may be warranted. The 2007 analysis showed that the average cost of biologic New Active Substance submissions was $557,000 while the median was $497,000, compared with an average cost of $420,000 and a median cost of $385,000 for pharmaceutical NAS submissions (Health Canada & Spearhead Management Canada Limited, 2007).

BGTD representatives indicated that the higher cost of biologics submissions reflects the greater complexity of these files, compared to pharmaceutical submissions. The 2011 updates to the cost recovery framework and user fees did not, however, reflect these differences, for several reasons identified by BGTD. In consultations, the biologics industry objected to the prospect of higher fees on the grounds that it would be disadvantaged by higher fees, and that investments in Canada would be negatively affected. It was also noted that a separate fee structure was inconsistent with international practices. An alternative fee, based on the combination costs of service delivery for both product lines, was contemplated but rejected on the grounds that it would disadvantage the pharmaceutical industry by creating a situation in which it would be
effectively cross-subsidizing biologics. Ultimately, the Cost Recovery Initiative Steering Committee decided to adopt the lower fees for pharmaceuticals for both pharmaceuticals and biologics, but agreed to review the issue as part of the next round of cost recovery consultations.

Health Canada is reviewing its costs, fees, and performance associated with the BP as per its commitment in the User Fee Proposal and the Regulatory Impact Analysis Statement associated with the Fees in Respect of Drugs and Medical Devices Regulations. Preliminary results are expected in 2014.

8.0 Conclusions and recommendations

Relevance

There is an ongoing need for continued oversight by Health Canada to help protect the health and safety of Canadians. Increased use of biologics is exposing more Canadians to the risks, as well as the benefits of these products. Health Canada’s role is consistent with federal and Health Canada roles and responsibilities.

The evaluation confirmed an ongoing need for government oversight of biologics in order to help protect the health and safety of Canadians. Biologics contribute significantly to the health of Canadians and represent an important component of the Canadian health care system. Moreover, while biologics are frequently used in the treatment of rare diseases, their use in treating more common, long-term conditions (such as diabetes, cardiovascular disease, digestive disorders and asthma) is growing. Currently, four of the five top-selling drugs in Canada, and five of the top ten, are biologics. As use of these products grows due to demographic factors, as well as marketing by industry, more Canadians will be exposed to the risks, as well as the benefits, of these products. Moreover, trends such as the emergence of innovative therapies and products, combination products, and globalization of the supply chain are creating uncertainties that further support the need for government intervention to help protect the health and safety of Canadians. Such a role, furthermore, is consistent with federal and Health Canada roles and responsibilities, as described in federal statutes and regulations, and aligns directly with Health Canada’s strategic outcome to inform Canadians and protect them from health risks associated with food, products, substances, and environments.

The BP is aligned with federal priorities to improve the safety of health products through regulatory modernization.

BP activities are well-aligned with federal priorities to strengthen consumer safety. The federal government has devoted substantial resources over the past decade to broader initiatives intended to improve the safety of health products, including biologics, through modernizing the regulatory framework for these products. Key principles of regulatory modernization include adopting a product lifecycle approach, whereby the risks and benefits of therapeutic products are assessed over their entire lifecycle; adopting regulatory interventions proportional to risk; and enhancing the transparency and openness of the regulatory system.
Performance — program implementation

Health Canada has developed comprehensive regulatory frameworks to address the risks associated with cells, tissues and organs and blood and blood components, and work is ongoing to develop regulations for orphan drugs and to modernize the existing vaccine regulations.

Over the period of the evaluation, Health Canada has made progress in implementing its planned activities and, in the process, has responded to several emergent issues and challenges. However, a number of unresolved issues and challenges remain.

Legislative and regulatory development

Over the period of the evaluation, Health Canada developed comprehensive regulatory frameworks to address the risks associated with CTO and blood and blood components. National CTO standards were implemented in 2003, and Phase I of the Safety of Human Cells, Tissues and Organs for Transplantation Regulations (the CTO Regulations) came into force in December 2007. The Regulations included provisions related to CTO establishment registration; quarantine; errors, accidents, and adverse reactions; reporting to Health Canada; and quality assurance systems, among others. Health Canada is continuing to develop Phase II of the CTO regulatory framework, which will include more comprehensive compliance monitoring and enforcement provisions, as well as surveillance and adverse reaction reporting strategies. Phase II will also extend to heart valves and dura mater; these products will transition from the Medical Devices Regulations to the CTO Regulations.

Health Canada is currently in the process of finalizing a new regulatory framework for blood and blood components, which will constitute its final response to the 1997 recommendations of the Commission of Inquiry on the Blood System in Canada (the Krever Commission). As with the CTO Regulations, Health Canada took a staged approach to developing the blood regulatory framework, which included implementing a new establishment licensing process for blood establishments; updating the plasmapheresis regulations; and implementing blood standards. The Blood Regulations were published in Canada Gazette II in October 2013 and are expected to come into force in October 2014.

Health Canada is currently developing a regulatory framework for the development, evaluation, and approval of orphan drugs, which are drugs (often biologics) developed specifically for the treatment of rare diseases. In addition, updates to the regulatory framework for vaccines for human use and for donor semen are planned for future phases of regulatory modernization. With respect to donor semen, BGTD is considering options to keep pace with new techniques for extraction, freezing, and storage that have been developed in the past few years. Although there have been a number of challenges to putting regulations in place under the Assisted Human Reproduction Act (AHRA), including a constitutional challenge by the Province of Quebec, policy discussions and analysis of options are currently underway.

Other emerging biologic therapies, such as stem cell therapy and gene therapy, are currently treated as drugs under existing regulation. This is similar to the US approach, but different from the EU, where a dedicated regulatory framework for advanced therapy medicinal products has
been in place since 2007. Both the US and the EU, unlike Health Canada, have established multi-disciplinary advisory committees that review and evaluate data relating to the safety, effectiveness, and appropriate use of advanced treatments, although it is important to note that the committee approach is used for all products, not just advanced therapies.

Health Canada currently treats SEBs as NDS under the existing regulatory framework. The biologics industry perceives a need for clearer guidance with respect to emerging biologic therapies, and favours including SEBs in Health Canada’s regulatory modernization initiatives. BGTD representatives noted that experience will inform whether regulatory amendments are necessary.

**Clinical trials**

Health Canada has taken numerous steps to strengthen the regulatory framework for clinical trials, but does not currently require sponsors to disclose the results of clinical trials.

Health Canada has strengthened the regulatory framework for clinical trials by implementing risk-based approaches to monitoring clinical trial adverse reaction reports, introducing an inspection program for clinical trial sites, and commissioning the development of new voluntary standards for Research Ethics Boards. In response to concerns that the requirement to file a CTA was posing an undue burden on researchers using PERs, Health Canada implemented regulations defining which types of basic clinical research studies involving PERs fall outside the clinical trial regulations, and which require a CTA.

Most recently, in May 2013, Health Canada launched a new public database of drug clinical trials it had authorized. Though mandatory for sponsors, the database contains more limited information than the registries that have been mandatory in the US since 1997 and the EU since 2004. Furthermore, unlike the US (and soon the EU), Health Canada does not require sponsors to disclose the results of clinical trials. Further enhancing the amount of clinical trial information it makes publicly available, including the results of clinical trials, would be consistent with Health Canada’s commitment to enhancing transparency and openness as part of regulatory modernization, and would further align its approach with its main international counterparts.

**Recommendation 1:**

Consistent with international trends and its commitment to enhancing transparency and openness under regulatory modernization, Health Canada should further enhance the amount of clinical trial information it makes publicly available, including the results of clinical trials.

**Submission review and market authorization**

BGTD has met its performance targets for first review of biologics submissions since 2006. It is unknown how frequently OSEs and LRP evaluations identify issues that could affect the quality or safety of a product, and it is unclear if the BP collects this information in a systematic way.
Health Canada achieved a major milestone with the coming into force of the *Fees in Respect of Drugs and Medical Devices Regulations* in April 2011. The Regulations updated user fees for various regulatory services, including submission review and drug establishment licensing, with the goal of restoring the cost-sharing ratio of 50% that existed when user fees were first introduced in 1995. The increase in revenues stemming from updated user fees is expected to contribute to a stable funding platform that will improve Health Canada’s ability to provide regulatory services.

That said, it is important to note that BGTD has met its performance targets for first review since 2006, well before updated user fees were implemented. Furthermore, while the timeliness of submission review has fluctuated over the period of the evaluation, in both 2011 and 2012, 100% of biologics NDS and SNDS review cycles were completed within the service standard.

BP representatives expressed concern that the updated user fees did not take into account the higher costs of biologics submissions compared to pharmaceutical submissions. These higher costs stem from the greater complexity of biologics submissions and from the extra costs associated with OSEs and the LRP. OSEs are routinely conducted for new product types and changes to biologics manufacturing processes and facilities as part of the review process; their purpose is to confirm the information in the submission and make sure that there are no previously unforeseen factors that could result in a poor-quality product or increase the likelihood in the future of an error or accident that could lead to a contaminated product. Data provided by BGTD show that OSEs require, on average, 220 hours of staff time ($18,600 in salary), as well as an average of $8,502 in travel costs. Between 2000 and 2005, eight Notices of Deficiency were issued based on the outcome of OSEs.

The LRP is a risk-based program covering both pre- and post-market stages. Given that biologics involve the use of living organisms that are inherently more variable, difficult to consistently produce and characterize, and more sensitive to changes in starting materials and manufacturing than chemically synthesized drugs, the LRP is intended to provide additional monitoring of these products to help ensure their safety and efficacy. Products subject to the LRP are assigned to one of four Evaluation Groups, each of which corresponds to a different level of regulatory oversight based on product risk levels. Data provided by BGTD indicate that there were 29.9 FTEs associated with the LRP in 2012-2013, representing salary costs of approximately $3.5 million.

The evaluation could not determine how frequently OSEs and LRP evaluation identify issues that could affect the quality or safety of a product, and it is unclear if the BP collects this information in a systematic way.

**Recommendation 2:**

*Health Canada should maintain data on the frequency with which OSEs and LRP evaluations identify issues with potential implications for product quality and safety. This information could help to demonstrate the importance of, and need for, these unique components of the BP.*

Like OSEs and the LRP, regulatory research is another unique element of the BP that does not exist within the Pharmaceuticals Program. The research performed is a combination of 1) forward-looking research to anticipate new issues in the regulation of biologics, and 2) tactical
method development and problem-solving. The former often informs policy development in emerging areas of regulation, whereas the latter supports the pre-market review, as well as the post-market functions of the BP through, for example, developing new methods to support the evaluation of biologics, or conducting laboratory analyses to support Inspectorate activities. Work is ongoing to develop a governance framework that will allow the research function to be a readily-available resource to all partner directorates in the BP, while still performing the type of forward-looking research that can inform policy development. Over the past several years, the research function has reportedly been encountering some significant resource challenges.

Post-market surveillance

Health Canada has taken numerous steps to improve post-market surveillance of biologics, while there are ongoing challenges with adverse reaction reporting for biologics and the use of adverse reaction report data. Health Canada lacks a standardized approach and centralized mechanism for systematically tracking its signal activities and its response to the recommended actions arising from completed signal assessments.

Over the period of the evaluation, Health Canada has taken a number of steps to improve post-market surveillance, including implementing electronic adverse reaction reporting for health care professionals and, more recently, for industry. Most recently, on December 6, 2013, Bill C-17, the Protecting Canadians from Unsafe Drugs Act (Vanessa’s Law) was announced and is currently in second reading. This legislation proposes changes to the Food and Drugs Act that are expected to improve Health Canada’s ability to collect post-market safety information, including a proposed amendment introducing mandatory reporting of adverse reactions by health care institutions. The CTO Regulations and the proposed new Blood Regulations both already include provisions for mandatory reporting by health care institutions for certain types of adverse reactions.

Despite progress in these areas, there remain some challenges associated with adverse reaction reporting for biologics and the use of adverse reaction report data by Health Canada. Some of these challenges stem from the fact that, in addition to Health Canada, the PHAC and the provinces and territories also have responsibilities for post-market surveillance of blood, CTO, and vaccines. This introduces the potential for confusion among stakeholders regarding adverse reaction reporting obligations, as well as the possibility of under-reporting to the Canada Vigilance Program, Health Canada’s adverse reaction reporting system. Although Health Canada and PHAC regularly collaborate to reconcile adverse reaction report data for these products in their respective databases, confidentiality provisions prevent Health Canada from directly accessing PHAC and provincial/territorial databases. As a result, Health Canada does not have access to comprehensive adverse reaction report data for these products, which limits the usefulness of these data for the purpose of post-market surveillance. Notably, the 2010 Lessons Learned Review on the PHAC/Health Canada response to the 2009 H1N1 pandemic recommended that the parties involved (PHAC, Health Canada, and the provinces and territories) finalize agreements on sharing vaccine surveillance information across jurisdictions and implement an integrated surveillance system for immunization, including monitoring adverse events.
Although Health Canada has begun developing and implementing strategies such as targeted surveillance and data mining to systematically monitor adverse reaction reports in the Canada Vigilance Program for potential safety signals, the latter is likely to have limited usefulness for post-market surveillance of biologics in the near term. This is because many biologic products are used in small populations and therefore are unlikely to generate a sufficient number of adverse reaction reports in the Canada Vigilance Database to support data mining. While Health Canada does carry out targeted surveillance using Canada Vigilance data for targeted adverse events in relation to specific, targeted drugs, it relies more extensively on other sources for post-market safety information, including international data, information provided by market authorization holders (e.g., PSURs), and individual case study reports. That said, as the use of biologics to treat more common conditions becomes more widespread, data-mining may become more important in future as a means of identifying potential safety signals.

Currently, Health Canada lacks a standardized approach and centralized mechanism for systematically tracking its signal activities and its response to the recommended actions arising from completed signal assessments. At present, this information is inconsistently maintained and highly dispersed across HPFB. A tracking tool for safety recommendations for pharmaceuticals has recently been introduced, and according to BP representatives, a system to monitor outcomes of biologics signals will be considered for future implementation. Given the potential implications for the health and safety of Canadians, a comprehensive, consistent, and centralized approach to information management for Health Canada’s post-market surveillance activities seems warranted.

**Recommendation 3:**

*Health Canada should improve its information systems for post-market surveillance and monitoring. In particular, Health Canada should develop and implement a comprehensive and centralized approach to information management for post-market surveillance activities. This should include a centralized mechanism for tracking signal activities related to biologics, including Health Canada’s response to the recommended actions arising from completed biologics signal assessments.*

Despite announcing plans to do so under the FCSAP, Health Canada has not implemented some elements of a strengthened approach to post-market surveillance that are in place elsewhere, namely the authority to compel manufacturers to submit RMPs and PSURs. However, the recently announced Bill C-17 proposes an amendment to the *Food and Drugs Act* that would allow Health Canada to require persons to provide information within their control for the purpose of assessing serious risks to health, and to require manufacturers to compile information, conduct new tests or studies, and/or monitor experience, for the purpose of obtaining additional information. Bill C-17 also proposes to authorize Health Canada to impose terms and conditions on market authorizations and to amend these terms and conditions when necessary.

While the latter authority is considerably broad, it is unclear if Health Canada has specific plans to compel RMPs in future. Another area of uncertainty is the extent to which Health Canada monitors manufacturers’ compliance with the conditions imposed as part of NOC/cs.
**Recommendation 4:**

Health Canada should examine whether there is an ongoing rationale for pursuing the authority to compel manufacturers to submit risk management plans as per its commitment under the FCSAP.

**Compliance and enforcement**

Health Canada has taken a number of steps to strengthen compliance and enforcement. Challenges remain related to GMP reporting by product line.

In the area of compliance and enforcement, Health Canada has strengthened clinical trial inspections by developing risk criteria for site selection; strengthened oversight over imported products through the National Border Integrity Program; introduced a GVP inspection program; and adopted a risk-based approach to GMP inspections of domestic drug establishments.

Health Canada and the FDA have recently launched an initiative under the RCC that aims to increase each country’s reliance on GMP inspection reports prepared by the other country. Currently, the initiative applies to sites in Canada and the US, although it may be expanded to other jurisdictions in the future. Although a key focus of the RCC initiative is the standardizing and sharing of GMP inspection reports, Health Canada and the FDA differ in their reporting approaches. While the FDA reports by product category, Health Canada aggregates GMP reporting for pharmaceutical, biologic and veterinary drugs. Achieving the objectives of the initiative may require a common approach to compliance reporting.

Bill C-17, which was announced on December 6, 2013, proposed amendments that would give Health Canada the power to recall therapeutic products from the market when they present an imminent or serious risk to health. The amendments also include increased fines and penalties up to a maximum of $5,000,000 and/or two years in prison. These amendments, if implemented, would address the concerns expressed by some key informants about what they perceive as the relatively limited enforcement options that are currently available to Health Canada.

**Communications and stakeholder engagement**

Health Canada has undertaken a number of initiatives to improve communications and stakeholder engagement.

Health Canada has undertaken a number of initiatives to improve communications and stakeholder engagement. For example, since 2005, Health Canada has provided the public with information about review decisions through SBD documents. In 2012, in part to address concerns expressed by the OAG that it was not disclosing information related to NOC/cs, rejections, and withdrawals of new drugs, Health Canada introduced the post-authorization activity table (PAAT). PAATs provide ongoing information about approved products. They include a brief summary of activities that affect the safe and effective use of the product, such as information related to submissions for a new use of the product (whether Health Canada’s decision was positive or negative), submissions filed in order to meet conditions (for products approved under the NOC/c Guidance), and regulatory decisions such as the cancellation of the DIN. Health Canada does not publish SBDs for negative decisions or otherwise provide information to the public about the reasons for negative decisions, unlike the FDA and the EMA.
However, beginning in 2014–2015, Health Canada will begin publishing summaries of post-market drug safety reviews.

To improve the quality and availability of easy-to-understand drug product labelling, Health Canada has enhanced the product monograph and introduced regulatory amendments under the Plain Language Labelling Initiative. At present, Health Canada has limited authority to require manufacturers to modify product labelling once a product has received a Notice of Compliance. This shortcoming is addressed by Bill C-17, which would give Health Canada the authority to require manufacturers to modify a product label or to modify or replace its package in order to prevent injury to health.

Over the period of the evaluation, Health Canada has disseminated risk and safety information through the “advisories, warnings and recalls” page on the MedEffect website and a variety of other dissemination mechanisms. In early 2013, Health Canada launched the Recalls and Safety Alerts Database, which includes an advanced search feature and a new format for risk communications. Health Canada indicated that it is currently in the process of reviewing its existing performance targets for the content development of risk communications and the dissemination of risk communications, and is looking at areas where more focused improvements in risk communications could be made. Health Canada also recently initiated an evaluation of its risk communications for health products, including biologics, following through on long-standing plans to assess the effectiveness of its risk communications products.

Health Canada provides a variety of opportunities for stakeholder engagement, such as holding public consultations on proposed guidance, policies, and regulatory amendments and establishing advisory committees to guide regulatory and policy development. In addition, Health Canada consults with industry through pre-submission meetings and the Bilateral Meeting Program (BMP). While these specific opportunities are not available to health care practitioners and consumers/patients, Health Canada indicated that it does meet with industry associations, hospital associations, and medical associations representing health care practitioners. Some external key informants expressed concern that the engagement and consultation process may favour industry over other stakeholders.

Performance — outcomes achieved

Over the period under evaluation, Health Canada has engaged in many activities that are expected to contribute to the outcomes of the BP. However, for various reasons, data to support definitive conclusions on outcomes achieved are relatively limited.

Immediate outcomes

There are opportunities to improve awareness and understanding of drug safety information among consumers and health professionals.

In the immediate term, Health Canada’s activities are expected to produce increased awareness and understanding by non-industry stakeholders of risks and benefits related to biologics. Surveys conducted between 2003 and 2007 identified opportunities to improve awareness among both consumers and health professionals of drug safety information available from Health
Canada, although information specific to biologics was not available. Health Canada is currently in the process of evaluating the effectiveness of its risk communications.

**There are opportunities to improve awareness and understanding of pre-market activities among industry.**

In the immediate term, Health Canada’s activities are expected to produce increased awareness and understanding among industry of Health Canada’s regulatory activities for biologics. The available evidence, though limited, points to some potential areas for improvement. Areas where greater clarity may be required include the classification of stem cell, gene therapy, and other emerging health products; naming of SEBs; classification of CTO products; classification of some combination products; and Health Canada’s use of foreign reviews and guidance in the review process.

**There are pre-market and post-market processes in place that are intended to help ensure that biologics are safe and effective.**

In the short term, Health Canada’s activities are also intended to produce increased safety and effectiveness of biologics. There are pre-market and post-market processes in place that are designed to help ensure that biologics are safe and effective, but no concrete evidence of improvements in these areas.

**The available data suggests that serious industry non-compliance is relatively uncommon. There are opportunities to improve compliance reporting by focusing to a greater extent on outcomes and disaggregating compliance reporting by product line.**

Finally, in the short term, Health Canada’s activities are expected to lead to increased industry compliance with regulatory requirements. The available data suggest that serious non-compliance is relatively uncommon. Over the period of the evaluation, however, Health Canada has not reported regularly or consistently on the nature, seriousness, frequency, or prevalence of non-compliances related to biologics, and has focused its reporting, instead, on quantifying activities and outputs. Furthermore, much of Health Canada’s compliance data, including GMP, GCP, and GVP compliance data, is aggregated across multiple product categories, encompassing human drugs and biologics.

That said, the Inspectorate has recently developed an annual inspection summary report that will be published on the Health Canada website. The 2012–2013 report includes a description of Inspectorate activities and outputs, describes the overall compliance rate of industry, and lists the common observations cited in non-compliant establishments. The report does not contain any information on actions taken by the Inspectorate in response to non-compliance, nor does it break down GMP, GCP and GVP compliance information by product category. However, inspection and compliance information for semen, blood and CTO are reported by product category.

There are number of challenges to disaggregating compliance reporting, including technical difficulties in extracting the necessary data. In addition, while the pre-market function of the BP is aligned around the product, this is not necessarily true of the compliance function, which is oriented around processes. Thus, a GMP inspection of a manufacturing facility that produces both pharmaceuticals and biologics focuses on the overall manufacturing process, not on the products...
manufactured there, and the inspection outcome is applicable to the facility as a whole. That said, similar constraints do not present themselves with respect to GCP inspections. Clinical trials involve a single product, which is either a pharmaceutical or a biologic, and therefore clinical trial inspection data could more easily be reported by product type. In the context of Health Canada’s current Program Activity Architecture, in which the Pharmaceuticals Program and the Biologics Program are distinct program areas, there is a need to report program-specific inspection and compliance data.

**Recommendation 5:**

Health Canada should build on its current approach to compliance reporting by increasing its emphasis on compliance and enforcement outcomes, and enhancing its ability to report biologics-specific GMP, GVP, and GCP inspection and compliance data.

**Intermediate outcomes**

The extent to which Health Canada activities have led stakeholders to adopt safe behaviours is unknown. Health Canada’s ongoing evaluation of the effectiveness of its risk communications may shed light on this question.

In the intermediate term, Health Canada activities are expected to lead stakeholders, in particular health care professionals and consumers, to adopt safe behaviours with respect to the use of biologics. Nonetheless, the extent to which Health Canada’s activities may influence these behaviours is unknown. Health Canada’s ongoing evaluation of the effectiveness of its risk communications may provide insights into the degree to which its activities have influenced stakeholder behaviour.

The use of scientific evidence and risk-benefit analysis (and/or risk-based analysis) is formally incorporated into Health Canada’s pre-market and post-market processes.

Health Canada activities are also expected to result in increased use of scientific evidence and risk-benefit analysis to inform decision making related to biologics. The use of scientific evidence and risk-benefit analysis is formally integrated into Health Canada’s Decision-Making Framework for Identifying, Assessing and Managing Health Risks, and also into various pre-market and post-market processes. Health Canada has established a number of Expert Advisory Committees to provide guidance on regulatory and policy development, and has implemented some, of their recommendations. For example, development of the CTO and Blood Regulations were both informed by input from committees of external experts.

Recognizing that policy and regulatory development is often a lengthy process, there are instances in which Health Canada’s response has taken longer than expected to implement. The overall timeliness of the biologics signal process (i.e., from signal detection to ultimate action taken by Health Canada) could not be determined.
In the intermediate term, Health Canada hopes to achieve a timely response to identified risks related to biologics. Recognizing that policy and regulatory development is often a lengthy process, the evaluation found some instances in which Health Canada’s response has taken longer than expected to implement. Both the CTO and the Blood Regulations, for example, took more time and resources to complete than originally planned.

Analysis of Health Canada’s signal data revealed that biologics signals are assigned for assessment in a timely fashion and that a large majority of biologics signal assessments are completed within the service standard of 130 days. Due to a limited number of cases, the evaluation was unable to draw conclusions about the overall timeliness of the biologics signal process (i.e., the total time elapsed from signal detection to ultimate action taken by Health Canada).

**Health Canada is actively engaged in a variety of international fora. Health Canada is viewed by international key informants as a constructive participant in bilateral and multilateral engagement.**

In the intermediate term, Health Canada expects to achieve increased international harmonization of regulatory requirements for biologics. Among many other international engagements, Health Canada is an official observer to and participant in the ICH; has developed MRAs on GMP compliance with a number of other jurisdictions; has formal information-sharing agreements with the FDA, Australia’s TGA, and the European Community; and participates with the FDA in the RCC, the overall goal of which is to better align the two countries’ regulatory approaches.

BGTD serves as a prequalification authority for the WHO’s Vaccine Prequalification Network, and is a founding member of the WHO’s Blood Regulators Network. BGTD also helped to develop the WHO’s GMP for Blood Establishments, contributed to the WHO’s guidance document on follow-on biosimilars, and was recently confirmed as a WHO Laboratory Collaborating Centre for Biologics to verify international standards for influenza vaccines. International key informants view Health Canada as a constructive participant in bilateral and multilateral engagement.

**Long-term outcomes**

**Health Canada’s activities have likely contributed to a reduced exposure to health risks and fewer adverse reactions.**

In the long term, Health Canada’s activities will likely contribute to reduced health risks and adverse events associated with the use of biologics. The available survey data show a high level of confidence among consumers in the safety of drugs and the regulatory system, though information specific to biologics is not available.

Ultimately, Health Canada hopes to achieve a sustainable, cost-efficient, responsive, and science-based regulatory system for biologics in Canada. The evaluation found that Health Canada uses scientific evidence and consults with stakeholders in policy and regulatory development. While recent updates to user fees for biologics help to support the sustainability of the regulatory system for biologic drugs, BP representatives noted that the fees did not consider the greater complexity of biologics submissions or the extra costs associated with OSEs and the LRP. Furthermore, other product lines such as CTO and blood products are not cost-recovered.
Performance — efficiency and economy

Program performance and financial information was insufficient to properly demonstrate efficiency and economy. HPFB has recently implemented a number of improvements to its approach to financial reporting, which should facilitate future analysis.

Changes in HPFB’s approach to financial reporting over the period of the evaluation made it challenging to consistently match BP expenditures and budgets, so as to compare and analyze this information over time. HPFB has recently restructured its financial reporting to comply with federal government requirements, which should improve the accuracy of this information and facilitate future analysis.

Activity-based financial reporting has not taken place since 2008–2009. Activity-based reporting is important to support activity-based costing, which in turn is important to analysing the efficiency with which program activities are carried out. HPFB undertook an activity-based costing exercise in 2007 to support the proposal for updated user fees, and used the results of this analysis to calculate unit costs for a variety of regulatory activities, including submission review.

The available data indicate that the timeliness of submission review has improved for biologics submissions under the new cost recovery framework. However, without analysing the unit costs of submission review and other cost-recovered activities, it is unclear if improvements in timeliness also represent improved efficiencies. In addition to enabling an assessment of the extent to which efficiencies may have been realized under the new cost recovery framework, such analysis would also assist the BP in identifying where future adjustments to the framework may be necessary. As such, it could update the analysis undertaken in 2007 to support adjustments to the cost recovery framework, which showed that cost of reviewing biologics submissions was considerably higher than the cost of reviewing pharmaceutical submissions. The 2011 updates to the cost recovery framework and user fees did not, however, reflect these differences.

HPFB is reviewing its costs, fees, and performance associated with the BP, as per its commitment in the User Fee Proposal and the Regulatory Impact Analysis Statement associated with the Fees in Respect of Drugs and Medical Devices Regulations.
## Appendix A – Evaluation Matrix

<table>
<thead>
<tr>
<th>Evaluation issues and questions</th>
<th>Indicators</th>
<th>Potential data sources</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SECTION 1: RELEVANCE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Issue #1: Continued need for the program</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is there a continued need for the BP?</td>
<td>Need for program identified/documentated</td>
<td>Document review:</td>
</tr>
<tr>
<td></td>
<td>Evidence of current/emerging human health and safety issues related to biologics</td>
<td>- Official government documents</td>
</tr>
<tr>
<td></td>
<td>Expert/stakeholder assessment of ongoing need</td>
<td>Key informant interviews (internal and external)</td>
</tr>
<tr>
<td></td>
<td>Responsiveness of BP to needs of Canadians</td>
<td>Document review:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Literature review</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Key informant interviews (external)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surveys of industry, patients/consumers, and physicians</td>
</tr>
<tr>
<td><strong>SECTION 1: RELEVANCE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Issue #2: Alignment with government priorities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the BP aligned with the priorities of the Government of Canada?</td>
<td>Extent to which the objectives of the BP are linked to Federal Government priorities</td>
<td>Document review:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- recent Speeches from the Throne/Budgets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Therapeutic Access Strategy (TAS), Therapeutic Product Safety Initiative (TPSI), Canada’s Access to Medicines Regime (CAMR), Food and Consumer Safety Action Plan (FCSAP), Cost Recovery Initiative (CRI)</td>
</tr>
<tr>
<td></td>
<td>Extent to which the objectives of the BP are linked to the strategic outcomes/priorities of Health Canada/HPFB</td>
<td>Document review:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- recent Health Canada Reports on Plans and Priorities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- HPFB Blueprint for Renewal reports, Regulatory Roadmap for Health Products and Food, and other related documents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- HPFB, BGTD, MHPD, Inspectorate strategic planning documents</td>
</tr>
<tr>
<td><strong>SECTION 1: RELEVANCE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Issue #3: Alignment with federal roles and responsibilities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the BP consistent with federal roles and responsibilities?</td>
<td>Extent to which the objectives of the BP are consistent with the legislative framework of the Federal Government</td>
<td>Document review:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- federal Acts and Regulations (Department of Health Act, Food and Drugs Act, etc., and relevant Regulations)</td>
</tr>
</tbody>
</table>
### SUMMATIVE EVALUATION OF THE BIOLOGICS PROGRAM (BP) – EVALUATION MATRIX

<table>
<thead>
<tr>
<th>Evaluation issues and questions</th>
<th>Indicators</th>
<th>Potential data sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>→ Extent to which the objectives of the BP are consistent with the legislative framework of Health Canada</td>
<td>Document review:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- federal Acts and Regulations (<em>Department of Health Act, Food and Drugs Act</em>, etc., and relevant Regulations)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- recent Health Canada Reports on Plans and Priorities</td>
<td></td>
</tr>
</tbody>
</table>

### SECTION 2: PERFORMANCE

**Issue #4: Achievement of expected outcomes**

Is the governance structure for BPA likely to support the achievement of expected outcomes?

| Is there an established governance structure to coordinate delivery of the BP? | → Extent to which internal and interdepartmental partners’ roles, responsibilities, accountabilities, and decision making authorities are documented and understood | Document review:  |
|                                                                          |                                | - descriptions of the organizational structures, mandates, and activities of BPA partners, as available from:  |
|                                                                          |                                | - Health Canada website  |
|                                                                          |                                | - health product regulation roles and responsibilities framework documents (2005; 2008)  |
|                                                                          |                                | - other internal documents (as available)  |
|                                                                          |                                | Key informant interviews (internal and external, i.e., other federal departments) |

→ Extent of collaboration among internal and interdepartmental partners, as evidenced by:
- existence of committees, working groups, and teams
- frequency of meetings of committees, working groups, and teams

| → Nature of industry and stakeholder involvement in BPA governance | Document review:  |
|                                                                | - BGTD, MHPD, Inspectorate, and HPFB operational, strategic, and business plans and performance reports  |
|                                                                | - committee/working group Terms of Reference (as available)  |
|                                                                | - meeting agendas/minutes (as available)  |
|                                                                | Key informant interviews (internal and external, i.e., other federal departments) |

→ Nature of industry and stakeholder involvement in BPA governance

### Has a performance measurement framework been designed and implemented?

| → Existence of performance measurement framework(s) | Document review:  |
|                                                   | - FCSAP and TPSI RMAFs; CRI PMEP  |
|                                                   | - BPA Summative Evaluation Framework |

→ Extent to which performance data are collected

| → Extent to which performance data are collected | Document review:  |
|                                               | - HPFB, BGTD, MHPD, and Inspectorate performance reports (e.g., quarterly reports, annual reports, business transformation reports)  |
|                                               | - FCSAP reports  |
|                                               | - Health Canada DPRs  |
|                                               | - Completed evaluations, e.g., Formative Evaluations of the TAS and the CAMR  |
|                                               | Key informant interviews (internal) |
### Evaluation of the Biologics Program – 1999-2000 to 2012-2013

May 2014

#### SUMMATIVE EVALUATION OF THE BIOLOGICS PROGRAM (BP) – EVALUATION MATRIX

<table>
<thead>
<tr>
<th>Evaluation issues and questions</th>
<th>Indicators</th>
<th>Potential data sources</th>
</tr>
</thead>
</table>
| Is the performance measurement framework used to support decision making? | Extent to which performance data are used to support decision making | Document review, for example:  
- HPFB, BGTD, MHPD, and Inspectorate operational, strategic, and business plans  
- MRAPs for relevant evaluations (e.g., TAS)  
Key informant interviews (internal) |

#### SECTION 2: PERFORMANCE

**Issue #4: Achievement of expected outcomes**

To what extent has the BP been implemented as planned?

| Has the Program effectively addressed challenges, emerging issues, and changing priorities? | Extent to which challenges, emerging issues, and changing priorities have been effectively addressed, for example:  
- classification of therapeutic products  
- combination products  
- ability to keep pace with scientific/technological advances (e.g., nanotechnology)  
- pharmacovigilance  
- subsequent entry biologics  
- personalized medicine  
- etc. | Document review (all documents)  
Literature review  
Key informant interviews (internal and external)  
Case studies (clinical trials, post-market, genetic therapies, contamination) |

| Have activities been implemented as planned? | Extent to which BPA have been implemented as planned, including planned activities for CAMR, TAS, TPSI, CRI, FCSAP  
 Enumeration of outputs (policies, guidelines, regulations, research, MOUs, etc.) produced, including outputs identified for CAMR, TAS, TPSI, CRI, FCSAP | Document review – For plans:  
- Official government documents  
- HPFB, BGTD, MHPD, and Inspectorate operational and strategic plans  
- RMAFS/PMEPs for FCSAP and TPSI; PMEP for CRI; TAS evaluation report; CAMR planning documents, and other planning documents as appropriate  
- planned spending data | Document review – For actual:  
- HPFB, BGTD, MHPD, and Inspectorate performance reports (e.g., quarterly reports, annual reports, business transformation reports)  
- FCSAP reports  
- Health Canada DPRs  
- TAS evaluation report  
- actual spending data  
- policies, guidelines, regulations, research, MOUs, etc. |

| Have requirements/ commitments to Central Agencies (i.e., Office of the Auditor General, Cabinet Directive on Streamlining Regulations, Policy on Public Consultation, Policy on Gender- Based Analysis) been addressed? | Extent to which requirements and commitments to Central Agencies have been addressed | Document review (all documents)  
Key informant interviews (internal and external) |
### SECTION 2: PERFORMANCE

#### Issue #4: Achievement of expected outcomes

**To what extent has progress towards expected outcomes been achieved?**

**Immediate outcomes**

<table>
<thead>
<tr>
<th>Evaluation issues and questions</th>
<th>Indicators</th>
<th>Potential data sources</th>
</tr>
</thead>
</table>
| To what extent is there increased awareness and understanding among external stakeholders of risks and benefits related to biologic products? | ▶ Number and nature of Health Canada communications to external stakeholders, by type and target group, including:  
  - Summary Basis of Decisions  
  - Product monographs  
  - Advisories, warnings, and recalls (for public and for health professionals)  
  - Canadian Adverse Reaction Newsletter  
  - Drug Recall Listings  
  - Canadian Adverse Reaction Database  
  - Products aimed at special or at-risk populations  
  - MedEffect subscription service  
  - Other information/communications  
  
  ▶ Existence of stakeholder lists and use of technology to deliver information to stakeholders  
  
  ▶ Use of partnerships to develop/deliver information to stakeholders  
  
  ▶ Extent and nature of Health Canada consultations with external stakeholders regarding risks and benefits of biologic products  
  
  ▶ Proportion of post market issues where a public communication piece is released  
  
  ▶ Extent of stakeholder awareness and use of the information made available by Health Canada, by product type  
  
  ▶ Stakeholder assessment of quality of Health Canada information/communications, in terms of:  
    - timeliness  
    - accessibility  
    - ease of understanding  
    - usefulness  
  
  ▶ Extent to which external stakeholders rely on Health Canada for risk/safety information versus other sources  
  
  ▶ Stakeholder perceptions of their level of awareness and understanding of risks related to biologic products  |                                                                                                                                                                                                         | Document/administrative data review, including publicly accessible data on Health Canada’s website  
  
  Document review  
  
  Document review  
  
  Key informant interviews (internal and external)  
  
  Document/administrative data review  
  
  Survey of health care providers  
  
  Survey of patients/consumers  
  
  Key informant interviews (external)  
  
  Focus group with CTO establishments  
  
  Survey of health care providers  
  
  Survey of patients/consumers  
  
  Key informant interviews (external)  
  
  Survey of health care providers  
  
  Survey of patients/consumers  
  
  Key informant interviews (external) |
<table>
<thead>
<tr>
<th>Evaluation issues and questions</th>
<th>Indicators</th>
<th>Potential data sources</th>
</tr>
</thead>
</table>
| To what extent is there increased awareness and understanding among industry of Health Canada’s regulatory framework for biologic products? | Number and nature of Health Canada communications, meetings, and consultations with industry stakeholders regarding the regulatory framework for biologic products, including:  
- Pre-submission meetings  
- Guidance documents  
- Bilateral Meeting Program  
- Consultations on proposed regulatory/policy changes and guidance for industry  
- Other communications and consultations | Document/administrative data review |
|                               | Use of technology to deliver information to industry                       | Document review                                      |
|                               | Use of partnerships/collaboration to develop/deliver information to industry | Document review                                      |
|                               | Extent of industry awareness and use of the information made available by Health Canada, by product type | Survey of industry  
Key informant interviews (external) |
|                               | Industry assessment of quality of Health Canada information and communications, in terms of:  
- timeliness  
- accessibility  
- ease of understanding  
- usefulness | Survey of industry  
Key informant interviews (external) |
|                               | Extent to which industry relies on Health Canada for regulatory information versus other sources | Survey of industry  
Key informant interviews (external) |
|                               | Industry perceptions of their level of awareness and understanding of Health Canada’s regulatory framework for biologic products | Survey of industry  
Key informant interviews (external)  
Focus group with CTO establishments |
| To what extent is there increased safety and effectiveness of biologic products? | Description of current approach to biologic product licensing, including extent to which process is risk-based | Document review  
Case study (clinical trials) |
|                               | Description of progressive licensing project, with emphasis on how progressive licensing is expected to improve safety and/or effectiveness | Document review  
Key informant interviews (internal) |
|                               | Extent and nature of pre-market activities, approaches, tools, and initiatives intended to increase safety and effectiveness, for example:  
- Performance targets/standards  
- Pre-submission meetings  
- Changes to requirements for clinical trials  
- Use of foreign reviews and post market data | Document/administrative data review  
Case study (clinical trials) |
|                               | Extent and nature of post market activities, approaches, tools, and initiatives intended to increase safety and effectiveness, for example:  
- Performance targets/standards  
- Pharmacovigilance plans/Risk management and mitigation plans | Document/administrative data review  
Case study (post-market) |
<table>
<thead>
<tr>
<th>Evaluation issues and questions</th>
<th>Indicators</th>
<th>Potential data sources</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Signal assessment and monitoring</td>
<td>Document/administrative data review, especially:</td>
</tr>
<tr>
<td></td>
<td>- Adverse reaction reporting and analysis</td>
<td>- TAS evaluation report</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- BGTD Annual Drug Submission Performance Reports</td>
</tr>
<tr>
<td></td>
<td>(Pre-market) Proportion of pre-market reviews for biologic products</td>
<td>Document/administrative data review</td>
</tr>
<tr>
<td></td>
<td>conducted within service standards</td>
<td>- BGTD Annual Drug Submission Performance Reports</td>
</tr>
<tr>
<td></td>
<td>(Pre-market) Trends in first decisions for biologics applications by outcome</td>
<td>Document/administrative data review</td>
</tr>
<tr>
<td></td>
<td>(Notice of Compliance, Notice of Deficiency, Notice of Non-Compliance, etc.)</td>
<td>- BGTD Annual Drug Submission Performance Reports</td>
</tr>
<tr>
<td></td>
<td>(Post market) Proportion of monitoring and surveillance activities</td>
<td>Document/administrative data review</td>
</tr>
<tr>
<td></td>
<td>addressed within service standards/targets</td>
<td>Case study (post-market)</td>
</tr>
<tr>
<td></td>
<td>(Post market) Trends in number of post market monitoring and surveillance</td>
<td>Document/administrative data review</td>
</tr>
<tr>
<td></td>
<td>activities</td>
<td>Case study (post-market)</td>
</tr>
<tr>
<td></td>
<td>(Post market) Trends in number and type of follow up actions as a result of</td>
<td>Document/administrative data review</td>
</tr>
<tr>
<td></td>
<td>each type of monitoring and surveillance activity</td>
<td>Case study (post-market)</td>
</tr>
<tr>
<td></td>
<td>Extent to which approval times are linked to safety (e.g., linkage between</td>
<td>Administrative data review</td>
</tr>
<tr>
<td></td>
<td>approval times and post market safety issues such as adverse reaction</td>
<td>Literature review</td>
</tr>
<tr>
<td></td>
<td>reports, withdrawals of product from market</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stakeholder satisfaction with timeliness of approval process and timeliness</td>
<td>Surveys of industry, health care providers, consumers/patients</td>
</tr>
<tr>
<td></td>
<td>of access to approved biologic products</td>
<td>Key informant interviews (external)</td>
</tr>
<tr>
<td></td>
<td>Stakeholder perceptions of safety and effectiveness of biologic products,</td>
<td>Literature review</td>
</tr>
<tr>
<td></td>
<td>including perceptions of adequacy of pre-market and post market processes</td>
<td>Document review</td>
</tr>
<tr>
<td></td>
<td>in place to ensure safety and effectiveness</td>
<td>Key informant interviews (external)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surveys of industry, health care providers and patients/consumers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Focus group with CTO establishments</td>
</tr>
<tr>
<td>To what extent is there increased</td>
<td>Description of new compliance and enforcement tools, approaches, and</td>
<td>Document review</td>
</tr>
<tr>
<td>industry compliance with Health</td>
<td>initiatives</td>
<td>Key informant interviews (internal)</td>
</tr>
<tr>
<td>Canada’s regulatory requirements</td>
<td>Adequacy of information technology tools to support compliance tracking</td>
<td>Document review</td>
</tr>
<tr>
<td>related to biologic products?</td>
<td></td>
<td>Key informant interviews (internal)</td>
</tr>
<tr>
<td></td>
<td>Adequacy of training related to biologic products delivered to Inspectorate</td>
<td>Document review</td>
</tr>
<tr>
<td></td>
<td>and RAPB staff</td>
<td>Key informant interviews (internal)</td>
</tr>
<tr>
<td></td>
<td>(Post market compliance) Number of regulated parties and proportion of</td>
<td>Document/administrative data review:</td>
</tr>
<tr>
<td></td>
<td>regulated parties inspected and/or monitored (manufacturers, clinical trials)</td>
<td>- Inspectorate reporting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Document/administrative data review:</td>
</tr>
<tr>
<td></td>
<td>(Post market compliance) Trends in number of inspections, compliance</td>
<td>- Inspectorate reporting</td>
</tr>
<tr>
<td></td>
<td>verifications, and other compliance/enforcement activities related to:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Good Manufacturing Practices</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Establishment Licences</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Clinical Trials/Good Clinical Practices</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Good Pharmacovigilance Practices</td>
<td></td>
</tr>
</tbody>
</table>
### SUMMATIVE EVALUATION OF THE BIOLOGICS PROGRAM (BP) – EVALUATION MATRIX

<table>
<thead>
<tr>
<th>Evaluation issues and questions</th>
<th>Indicators</th>
<th>Potential data sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Adverse reaction reporting&lt;br&gt;- Border integrity&lt;br&gt;- Controlled Drugs and Substances&lt;br&gt;- Post Market Reporting Compliance&lt;br&gt;- Etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Post market compliance) Trends in number and type of non-compliances found through each type of inspections and compliance verifications</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Document/administrative data review: &lt;br&gt;- Inspectorate reporting</td>
<td></td>
</tr>
<tr>
<td>(Post market compliance) Trends in number and outcomes of compliance and enforcement actions, including:&lt;br&gt;- Education/information&lt;br&gt;- Voluntary actions by industry&lt;br&gt;- Health Canada initiated/ordered recalls&lt;br&gt;- Product removals/seizures&lt;br&gt;- Monetary penalties assessed&lt;br&gt;- Import alerts and interventions at the border&lt;br&gt;- Etc.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Document /administrative data review: &lt;br&gt;- Inspectorate reporting</td>
<td></td>
</tr>
<tr>
<td>Proportion of regulatory/enforcement actions addressed within service standards/targets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Document /administrative data review: &lt;br&gt;- Inspectorate reporting</td>
<td></td>
</tr>
</tbody>
</table>

### SECTION 2: PERFORMANCE

**Issue #4: Achievement of expected outcomes**

To what extent has progress towards expected outcomes been achieved?

**Intermediate outcomes**

| To what extent do external stakeholders adopt safe behaviours associated with biologic products? | Extent to which external stakeholders report using Health Canada risk communications for decision making | Key informant interviews (external, especially health care practitioners/facilities, patient/consumer groups.)<br>Surveys of health care providers and patient/consumer groups |
|                                                                                                  | Number of stakeholders who report changes in behaviours due to Health Canada’s risk communications, for example:<br>- physicians/health care providers who report changing their prescription behaviour | Survey of health care providers<br>Key informant interviews (external)<br>Literature review |
|                                                                                                  | Trend data on improper or unsafe use of biologic products, including number and characteristics (type, severity, age, gender, etc.) of reported incidents | Literature review<br>Document review (if data available)<br>Key informant interviews (external, especially health care practitioners/facilities and patient/consumer groups<br>Surveys of physicians and patient/consumer groups |

To what extent is there increased use of scientific evidence and risk-benefit analysis?

| Description of Health Canada’s approach to decision making, including extent to which approach is risk-based | Document review<br>Key informant interviews (internal) |
## SUMMATIVE EVALUATION OF THE BIOLOGICS PROGRAM (BP) – EVALUATION MATRIX

<table>
<thead>
<tr>
<th>Evaluation issues and questions</th>
<th>Indicators</th>
<th>Potential data sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>by Health Canada to inform decision making?</td>
<td>Extent and nature of Health Canada’s post market activities to increase use of scientific evidence and risk-based analysis to inform decision making, for example: - Pharmacovigilance Plans - Risk Management and Mitigation Plans - Periodic Safety Update Reports - Canada Vigilance Program - Laboratory activities - Mandatory Adverse Reaction Reporting by institutions - Drug Safety and Effectiveness Network research activities</td>
<td>Document/administrative data review&lt;br&gt;Case study (post-market)</td>
</tr>
<tr>
<td></td>
<td>Number of safety signals generated through post market signal detection activities, including: - Environmental scanning - Evaluation of foreign post market data - PSUR reviews - Monitoring of adverse reaction reports - DSEN research activities</td>
<td>Document/administrative data review&lt;br&gt;Case study (post-market)&lt;br&gt;Key informant interviews (internal)</td>
</tr>
<tr>
<td></td>
<td>Extent to which information gathered through post market signal detection activities is used to inform decision making: - number and nature of responses taken in response to risks identified through post market signal detection activities</td>
<td>Document/administrative data review&lt;br&gt;Case study (post-market)</td>
</tr>
<tr>
<td></td>
<td>Extent to which recommendations of expert/scientific advisory groups are used to inform and develop policy/regulatory responses</td>
<td>Document review:&lt;br&gt;- Recommendations of expert/scientific advisory groups compared against policies, guidelines, regulations developed</td>
</tr>
<tr>
<td></td>
<td>Extent to which scientific research is used in regulatory framework development (regulations, guidance, Standard Operating Procedures)</td>
<td>Document review&lt;br&gt;Key informant interviews (internal/external)</td>
</tr>
<tr>
<td></td>
<td>Stakeholders’ perceptions of extent to which use of scientific evidence and risk-based analysis to inform decision making has increased</td>
<td>Key informant interviews/consultations (external and internal)&lt;br&gt;Surveys of industry, health care providers, and patients/consumers</td>
</tr>
<tr>
<td>To what extent is there a timely regulatory system response to identified risks?</td>
<td>(Overall regulatory/policy response) Description of regulatory process</td>
<td>Document review</td>
</tr>
<tr>
<td></td>
<td>(Overall regulatory/policy response) Elapsed time between initial identification of biologic product-related risks and policy/regulatory response by Health Canada</td>
<td>Document review (if information is available)&lt;br&gt;Case study (post-market)</td>
</tr>
<tr>
<td></td>
<td>(Response to risks identified through post market activities) Proportion of post market actions undertaken within service standards</td>
<td>Document/administrative data review:&lt;br&gt;- Inspectorate/MHPD reporting</td>
</tr>
<tr>
<td></td>
<td>Internal and external stakeholder perceptions of timeliness of Health Canada’s response to identified risks associated with biologic products</td>
<td>Key informant interviews/consultations (external and internal)&lt;br&gt;Survey of industry, health care providers, and patients/consumers</td>
</tr>
</tbody>
</table>
**SUMMATIVE EVALUATION OF THE BIOLOGICS PROGRAM (BP) – EVALUATION MATRIX**

<table>
<thead>
<tr>
<th>Evaluation issues and questions</th>
<th>Indicators</th>
<th>Potential data sources</th>
</tr>
</thead>
</table>
| To what extent is Canada’s regulatory framework for biologic products harmonized with international approaches? | ‣ Extent to which main features of Canada’s regulatory framework for biologic products is harmonized with that of other jurisdictions | Literature review/Key issues analysis:  
- comparison of main features of Canada’s regulatory framework with that of selected other jurisdictions (EU, US, Australia, UK)  
Key informant interviews (internal and external)  
Case studies (post-market, clinical trials, genetic therapies, contamination) |
| | ‣ Description of program’s decision making process regarding harmonization (especially factors considered in decision whether to harmonize) | Key informant interviews (internal) |
| | ‣ Extent to which Health Canada participates in international bodies, initiatives, boards, etc. | Document review  
Key informant interviews (internal) |
| | ‣ Number of international standards, policies, and guidelines adopted by Canada | Document review |
| | ‣ Extent of Health Canada contribution to development of international standards, policies, and guidelines | Document review  
Key informant interviews (internal) |
| | ‣ Extent to which Health Canada is recognized as a responsible biologic product regulator and scientific expert (nationally and internationally), as evidenced by:  
- Requests for information sharing by provinces/territories, other countries, and international organizations  
- Level of acceptance of Canadian laboratory expertise  
- Extent to which Health Canada experts participate on multilateral/international expert bodies | Document review  
Literature review  
Key informant interviews |

| To what extent is there reduced exposure to identified risks associated with the use of biologic products? | ‣ Trends in post market enforcement actions due to identified risks for authorized and unauthorized biologic products | Document/administrative data review:  
- Inspectorate data |
| | ‣ Trends in ratio of number of serious adverse reaction reports to total number of adverse reaction reports | Document/administrative data review  
- MHPD data |
| | ‣ Number of approved biologic products removed from the marketplace due to safety concerns | Document/administrative data review  
- Inspectorate data |
| | ‣ Number of unlicensed and counterfeit biologic products removed from the marketplace | Document/administrative data review  
- Inspectorate rate |
| | ‣ Expert assessment of changes in exposure to health risks related to biologic products | Key informant interviews (internal and external)  
Literature review |

**SECTION 2: PERFORMANCE**

**Issue #4: Achievement of expected outcomes**

To what extent has progress towards expected outcomes been achieved?

**Long term outcomes**

To what extent have adverse events associated with the use of biologic products been reduced? | ‣ Trends in number and severity of adverse drug reaction reports over time | Document/administrative data review  
Key informant interviews (internal) |
| | ‣ Rate of morbidity/mortality related to biologic products | Document/administrative data review (if available) |
### Evaluation issues and questions

| To what extent is there increased public confidence in biologic products and the related regulatory system? | Level of public confidence in safety of biologic products and the related regulatory system | Document review:  
- Health Canada public opinion research (if available)  
- Health Canada DPRs  
Key informant interviews (external) |
| To what extent is there a sustainable, cost-efficient, responsive, and science-based regulatory system for biologic products in Canada? | Number of requests for implementation of a similar safety system internationally | Document review |
| To what extent is there a sustainable, cost-efficient, responsive, and science-based regulatory system for biologic products in Canada? | Cumulative evidence from all outcome indicators | All data sources |

### SECTION 2: PERFORMANCE

#### Issue #4: Achievement of expected outcomes

| Were there any unintended consequences, either positive or negative, of the BP? | Unintended consequences identified by internal and external stakeholders | Key informant interviews/consultations (internal and external)  
Survey of industry  
Survey of stakeholders |

#### SECTION 2: PERFORMANCE

#### Issue #5: Efficiency and Economy

| Were BP resources used as planned? What accounted for overruns or lower-than-planned expenditures? | Comparison of planned versus actual spending for components of BPA and explanations for variances | Administrative data review, for example:  
- planned versus actual spending, SAP data, financial derivation reports, management variance reports (if available)  
Key informant interviews (internal) |
| Are there lower-cost approaches to producing outputs of the BP? | Extent to which existing resources could be used to produce outputs at lower cost  
Availability/accessibility of other, lower cost resources to produce outputs | Key informant interviews (internal)  
Document review |
| Are there alternate ways to achieve similar results at lower cost? | Approaches used in other jurisdictions and their costs  
Internal and external stakeholder assessment of other options | Literature review  
Case studies (all)  
Key informant interviews/consultations (internal and external) |
Appendix B – List of References

Cassels, A. (2012). Most of our prescription drugs are manufactured overseas — but are they safe? Canadian Medical Association Journal, 184(14), 1648.


GoC. (2008a). Bill C-51: An act to amend the Food and Drugs Act and to make consequential amendments to other Acts.
GoC. (2013c). Government of Canada Response to the Standing Senate Committee on Social Affairs, Science and Technology entitled Canada’s Clinical Trial Infrastructure: A Prescription for Improved Access to New Medicines.
Health Canada. (n.d.). OSE vs GMP: Background Information.

May 2014 124


HPFB. (2007a). Blueprint for Renewal II.


HPFB. (2012b). HPFB international activities: Inventory of significant international activities in HPFB (draft, updated April 2012).


May 2014


RMOD. (2013). Program Executive Committee (PEC) Lessons Learned.


TPD. (2007). Drug licensing process.

TPD. (2010a). Introduction to the current system (drug regulation in Canada).


TPD. (2012). Frequently Asked Questions: Summary Basis of Decision (SBD) project: Phase II.


Von Tigerstrom, B. (2012). How to Build (and Regulate) a Body Part: Regulating Tissue Engineering in Canada. *Available at SSRN.*


## Table 1: Number of CTAs received and approved, human drugs and biologics (2004–2012)

<table>
<thead>
<tr>
<th>Year</th>
<th>Human drugs</th>
<th></th>
<th>Biologics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># received</td>
<td># approved (NOLs)</td>
<td># received</td>
<td># approved (NOLs)</td>
</tr>
<tr>
<td>2004</td>
<td>1730</td>
<td>1677</td>
<td>258</td>
<td>229</td>
</tr>
<tr>
<td>2005</td>
<td>1732</td>
<td>1658</td>
<td>239</td>
<td>210</td>
</tr>
<tr>
<td>2006</td>
<td>1685</td>
<td>1621</td>
<td>272</td>
<td>245</td>
</tr>
<tr>
<td>2007</td>
<td>1724</td>
<td>1633</td>
<td>278</td>
<td>253</td>
</tr>
<tr>
<td>2008</td>
<td>1613</td>
<td>1579</td>
<td>267</td>
<td>232</td>
</tr>
<tr>
<td>2009</td>
<td>1400</td>
<td>1341</td>
<td>266</td>
<td>247</td>
</tr>
<tr>
<td>2010</td>
<td>1191</td>
<td>1162</td>
<td>272</td>
<td>263</td>
</tr>
<tr>
<td>2011</td>
<td>1181</td>
<td>1133</td>
<td>325</td>
<td>297</td>
</tr>
<tr>
<td>2012</td>
<td>1210</td>
<td>1160</td>
<td>320</td>
<td>298</td>
</tr>
</tbody>
</table>

% change, 2004–2012: Human drugs -30%, Biologics -31%

Sources: (BGTD, 2010a; TPD, 2008a, 2008b, 2010a) and data provided by Health Canada

## Table 2: Signal detection outcomes, biologics — MBB SIC WG (2008–2012)

<table>
<thead>
<tr>
<th>Signal Detection Outcomes</th>
<th>Number</th>
<th>%</th>
<th>Combined %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dismissed</td>
<td>6,288</td>
<td>96.7%</td>
<td>96.9%</td>
</tr>
<tr>
<td>Dismissed before preliminary review</td>
<td>6,288</td>
<td>96.7%</td>
<td></td>
</tr>
<tr>
<td>Dismissed before signal prioritization</td>
<td>1</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>Dismissed by signal prioritization committee</td>
<td>15</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>Total dismissed</td>
<td>6,304</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other actions

<table>
<thead>
<tr>
<th>Other actions</th>
<th>Number</th>
<th>%</th>
<th>Combined %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue monitoring / monitor in future PSUR / no further assessment</td>
<td>133</td>
<td>2.0%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Ad hoc request (AHR) / gap analysis</td>
<td>10</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>PSUR</td>
<td>4</td>
<td>0.1%</td>
<td></td>
</tr>
<tr>
<td>Other (N/A, blank, forward to MHPSEIB, BGTD, other)</td>
<td>19</td>
<td>0.3%</td>
<td></td>
</tr>
<tr>
<td>Total other</td>
<td>166</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Prioritized for signal assessment

<table>
<thead>
<tr>
<th>Prioritized</th>
<th>Number</th>
<th>%</th>
<th>Combined %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>18</td>
<td>0.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Medium</td>
<td>10</td>
<td>0.2%</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Prioritized</td>
<td>7</td>
<td>0.1%</td>
<td></td>
</tr>
<tr>
<td>Total prioritized</td>
<td>35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total | 6,505 |

Source: MBB_SIC_WG_tracking_2012-07-09.xls – worksheets “Prelim. Assessment Completed” and “No Action”

## Table 3: Sources for signal assessments, biologics (2005–2012)

<table>
<thead>
<tr>
<th>Sources</th>
<th># of signal assessments</th>
<th>% of total</th>
<th>% (combined)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>International regulator or agency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US (FDA)</td>
<td>18</td>
<td>8.8%</td>
<td>9.7%</td>
</tr>
<tr>
<td>EMEA</td>
<td>1</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>Health Canada (mechanisms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSUR</td>
<td>18</td>
<td>15.9%</td>
<td></td>
</tr>
<tr>
<td>CADRIS</td>
<td>4</td>
<td>3.5%</td>
<td>20.4%</td>
</tr>
<tr>
<td>Pre-market submission</td>
<td>1</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>Previous review</td>
<td>1</td>
<td>0.9%</td>
<td></td>
</tr>
</tbody>
</table>

* Combined % indicates the percentage of total signal assessments across all sources.
### Table 3: Sources for signal assessments, biologics (2005–2012)

<table>
<thead>
<tr>
<th>Sources</th>
<th># of signal assessments</th>
<th>% of total</th>
<th>% (combined)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Canada (body)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBB SIC WG</td>
<td>20</td>
<td>17.7%</td>
<td>19.5%</td>
</tr>
<tr>
<td>Vaccine Vigilance Working Group</td>
<td>1</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>MHPD</td>
<td>1</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>Other sources</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAH</td>
<td>43</td>
<td>38.1%</td>
<td>-</td>
</tr>
<tr>
<td>Literature</td>
<td>5</td>
<td>4.4%</td>
<td>-</td>
</tr>
<tr>
<td>Public Health Agency of Canada (PHAC) / Transfusion Transmitted Injuries Surveillance System</td>
<td>4</td>
<td>3.5%</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>4.4%</td>
<td>-</td>
</tr>
<tr>
<td>Source not indicated</td>
<td>9</td>
<td>8.0%</td>
<td>-</td>
</tr>
<tr>
<td>Total number of signal assessments</td>
<td>113</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Source: MBBNHPB activity signal tracking (2005-12) (Excel Spreadsheet). Filename: MBBNHPB_Signal Tracking_yyyy-mm-dd to yyyy-mm-dd

Note: Columns will not sum to total because signal assessments may have multiple sources. Percent of total may not equal combined percentage because the latter counts only whether or not the signal assessment was sourced from an international regulator, a Health Canada mechanism, or a Health Canada body. Differences in percentages reflect the fact that some signal assessments were sourced from multiple international regulators or Health Canada mechanisms or bodies.

### Table 4: Recommendations resulting from completed signal assessments, biologics (2005–2012)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Count</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard monitoring</td>
<td>32</td>
<td>28.3%</td>
</tr>
<tr>
<td>Request additional safety information</td>
<td>29</td>
<td>25.7%</td>
</tr>
<tr>
<td>Recommend changes to the product labelling</td>
<td>24</td>
<td>21.2%</td>
</tr>
<tr>
<td>Enhanced monitoring</td>
<td>18</td>
<td>15.9%</td>
</tr>
<tr>
<td>Risk communication</td>
<td>6</td>
<td>5.3%</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>2.7%</td>
</tr>
<tr>
<td>Issue Analysis Summary</td>
<td>1</td>
<td>0.9%</td>
</tr>
<tr>
<td>DSEN proposal</td>
<td>1</td>
<td>0.9%</td>
</tr>
<tr>
<td>No recommendation recorded</td>
<td>26</td>
<td>23.0%</td>
</tr>
<tr>
<td>Total</td>
<td>113</td>
<td>-</td>
</tr>
</tbody>
</table>

Source: MBBNHPB activity signal tracking (2005-12) (Excel Spreadsheet). Filename: MBBNHPB_Signal Tracking_yyyy-mm-dd to yyyy-mm-dd

Note: Signal assessments may result in more than one recommendation; therefore, columns will not sum.

### Table 5: Service standards for post-market activities

<table>
<thead>
<tr>
<th>Post-market activity</th>
<th>Target days to completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction reports</td>
<td></td>
</tr>
<tr>
<td>Priority initial report (death or life-threatening outcome)</td>
<td>15</td>
</tr>
<tr>
<td>Initial report</td>
<td>42</td>
</tr>
<tr>
<td>All initial and follow-up reports, standard and priority</td>
<td>84</td>
</tr>
<tr>
<td>Other post-market activities</td>
<td></td>
</tr>
<tr>
<td>Signal Assessment</td>
<td>130</td>
</tr>
<tr>
<td>RMP review</td>
<td>90</td>
</tr>
<tr>
<td>PSUR screening (Level I)</td>
<td>30</td>
</tr>
<tr>
<td>PSUR review (Level II)</td>
<td>90</td>
</tr>
<tr>
<td>Ad Hoc Reviews</td>
<td>60</td>
</tr>
<tr>
<td>Advertising Issue Assessment</td>
<td>15</td>
</tr>
</tbody>
</table>

Source: Health Canada, 2011c; MHPD, 2012b

Note: Performance targets for adverse event/reaction reports are from time of receipt to time of completion, in calendar days. Performance targets for other activities are from time of assignment to time of completion, in working days.
<table>
<thead>
<tr>
<th>Table 6: RMPs received and completed by MHPD (2009–2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RMPs received</strong></td>
</tr>
<tr>
<td>Number of RMP without pre-market submission</td>
</tr>
<tr>
<td>Number of RMP with pre-market submission</td>
</tr>
<tr>
<td><strong>Total RMPs received</strong></td>
</tr>
<tr>
<td><strong>RMPs completed</strong></td>
</tr>
<tr>
<td>Number of RMPs without pre-market submission</td>
</tr>
<tr>
<td>Number of RMPs with pre-market submission</td>
</tr>
<tr>
<td><strong>Total RMPs completed</strong></td>
</tr>
<tr>
<td>Source: Data provided by Health Canada.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 7: PSURs received and completed by MHPD (2009–2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PSURs received (solicited and unsolicited)</strong></td>
</tr>
<tr>
<td>Number of PSUR L1</td>
</tr>
<tr>
<td>Number of PSUR L2</td>
</tr>
<tr>
<td><strong>Total PSURs received</strong></td>
</tr>
<tr>
<td><strong>PSURs completed (solicited and unsolicited)</strong></td>
</tr>
<tr>
<td>Number of PSUR L1</td>
</tr>
<tr>
<td>Number of PSUR L2</td>
</tr>
<tr>
<td><strong>Total PSURs completed</strong></td>
</tr>
<tr>
<td>Source: Data provided by Health Canada.</td>
</tr>
</tbody>
</table>
Table 8: Summary of research findings relating to stakeholder awareness and understanding of risks related to human drugs and biologics

<table>
<thead>
<tr>
<th>Survey</th>
<th>Target</th>
<th>Relevant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public opinion survey on key issues pertaining to post-market surveillance of marketed health products in Canada (Decima Research, 2003)</td>
<td>Public (n=1,500)</td>
<td><strong>Perceptions of drug safety</strong>&lt;br&gt;• Most consumers (84%) are confident in the safety of prescription drugs, with 61% believing such drugs are generally safe, and 23% stating they are very safe. A similar proportion of consumers (85%) expressed confidence in the systems and safeguards in place to ensure the safety of prescription drugs for sale in Canada.&lt;br&gt;• Consumers are generally confident in the safety of non-prescription drugs (75%), with 62% believing such drugs are generally safe, and 14% believing they are very safe. <strong>Source of new drug safety information</strong>&lt;br&gt;72&lt;br&gt;• Among those consumers who look for new safety information for health products they are already taking (n=1,171), very few (3%) consumers (unaided) identified Health Canada’s website as a source for this information.&lt;br&gt;• When aided, 69% of all consumers said they were aware of Health Canada’s Public Advisories and Warnings. Most of these consumers (62%) were aware of this information being issued through the media, while about 31% of all consumers were aware of new drug safety information on Health Canada’s website (2003, p. 29,31).&lt;br&gt;• Among those consumers who had used Health Canada’s website to look for new drug safety information in the previous 6 months (n=125 or 8% of total), the vast majority (91% or 114) were satisfied with Health Canada’s website as a source of drug safety information (2003, pp. 30–31).</td>
</tr>
<tr>
<td>Health professionals (n=551)</td>
<td><strong>Familiarity with new drug safety information sources:</strong>&lt;br&gt;Manufacturers-issued <em>Dear Health Professional Letters (DHPLs)</em>&lt;br&gt;• Just over half (54%) of the health professionals indicated they were either very familiar or somewhat familiar with manufacturer-issued <em>Dear Health Professional Letters (DHPLs)</em> (2003, p. 47).&lt;br&gt;• Among the health professionals who had used this source in the past 12 months (n=126 or 23%) most did so occasionally (57%) or rarely (25%), and when accessing the material, they tended to read it selectively (49%) or thoroughly (33%) (2003, p. 51).&lt;br&gt;• Among the health professionals who had used this source in the past 12 months, most (86%) indicated they were satisfied with the source because it was a good source of information (51%), contained current/up-to-date information (35%), and gave them the information/answers they wanted (27%) (2003, pp. 53–54).&lt;br&gt;Health Canada-issued DHPLs&lt;br&gt;• 42% of health professionals were ether very or somewhat familiar with Health Canada-issued DHPLs (2003, p. 47).&lt;br&gt;• Among the health professionals who had used this source in the past 12 months (n=88 or 16%), most did so occasionally (52%) or rarely (31%). When doing so, they tended to read selectively (45%), read thoroughly (29%), or glance through it (26%) (2003, p. 51).&lt;br&gt;• Among the health professionals who had used this source in the past 12 months, most (84%) indicated they were satisfied with the source because it was a good source of information (55%), contained current/up-to-date information (35%), and gave them the information/answers they wanted (24%) (2003, pp. 53–54).&lt;br&gt;Canadian Adverse Reaction Newsletter&lt;br&gt;• Just over half (53%) of the health professionals were very or somewhat familiar with the Canadian Adverse Reaction Newsletter (2003, p. 47).&lt;br&gt;• Among the health professionals who had used this source in the past 12 months (n=97 or 18%), most did so occasionally (52%) or rarely (31%). When doing so, they tended to read selectively (59%), glance through it (24%), or read it thoroughly (18%) (2003, p. 51).&lt;br&gt;• Among the health professionals who had used this source in the past 12 months, the vast majority (90%) indicated they were satisfied with the source</td>
<td></td>
</tr>
</tbody>
</table>

---

72 Includes natural health products (NHPs). Reported data are drawn from the survey report and not the survey’s dataset, and, therefore, it is not possible disaggregate prescription and non-prescription drugs from NHPs.
### Table 8: Summary of research findings relating to stakeholder awareness and understanding of risks related to human drugs and biologics

<table>
<thead>
<tr>
<th>Survey</th>
<th>Target</th>
<th>Relevant findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>because it was a good source of information (49%), contained current/up-to-date information (40%), and gave them the information/answers they wanted (30%) (2003, pp. 53–54).</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Health Canada’s online drug safety advisories</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• About 4 in 10 (38%) were familiar with Health Canada’s online drug safety advisories (2003, p. 47).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Among those who had used this source in the past 12 months (n=65 or 12%), most did so occasionally (52%) or rarely (39%). When doing so, they tended to read selectively (52%), read thoroughly (23%), or glance through it (23%) (2003, p. 51).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Among the health professionals who had used this source in the past 12 months, most (82%) indicated they were satisfied with the source because it was a good source of information (49%), contained current/up-to-date information (26%), and gave them the information/answers they wanted (28%) (2003, pp. 53–54).</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Health Canada electronic mailing list</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Very few (11%) were aware of Health Canada’s electronic mailing list, and even fewer (n=9 or 2%) had accessed this source in the past 12 months (2003, pp. 47, 51).</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>ADRs</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 39% of health professionals consider Health Canada the best source of information on ADRs (2003, p. 61).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 88% of health professionals perceive ADRs as a somewhat or very serious problem.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 36% of health professionals said they would report ADRs in all situations, while 24% mentioned they would not report an ADR if it expected/well-known, or was too minor or trivial (23%).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Overall, just over half (55%) of the health professionals were aware of how to report an ADR; higher levels of awareness were found among specific health professions, such as pharmacists (92%) and, to a lesser degree, physicians (63%) (2003, pp. 83–84).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Among the health professionals who had filed an ADR in the past year (n=108), most (56%) mailed/faxed the form to Health Canada or contacted the drug manufacturer (48%).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Most health professionals support the need for mandatory reporting of ADRs in Canada, though opinion is divided among physicians (Decima Research, 2003, p. 90).</td>
</tr>
<tr>
<td>Final report: 2006 General public opinion survey on key issues pertaining to post-market surveillance of marketed health products in Canada (Follow-up to 2003 survey) (Decima Research, 2006)</td>
<td>Public (n=1,513)</td>
<td><strong>Perceptions of drug safety</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Most respondents perceived prescription drugs as being safe (86%), including 20% who felt these drugs were very safe.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Most respondents also felt non-prescription drugs were safe (75%), including 12% who felt they were very safe (2006, p. 15).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• About 78% of respondents expressed confidence in how the federal government monitors and regulates drug safety and effectiveness (2006, p. 16).</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>New drug safety information</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 36% of respondents were aware of Health Canada’s website as a source of new drug safety information. Among those who had accessed Health Canada’s website in the past six months (n=147), most looked for drug information (57%) or ADR information (34%) (2006, pp. 29–30).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• More commonly (62%), respondents were aware of public advisories and warnings issued through the media (2006, p. 29).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Very few respondents (1% or n=82) had subscribed to the MedEffect e-Notice. Among those who had not, most stated it was not very likely (29%) or not at all likely (38%) they would subscribe to it (2006, p. 31)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• About one quarter of respondents were aware Health Canada collects reports about adverse reactions from consumers (2006, p. 36).</td>
</tr>
<tr>
<td>Survey</td>
<td>Target</td>
<td>Relevant findings</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>--------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Adverse Reaction Reporting - Survey with Health Professionals</td>
<td>Health professionals (n=1,108)</td>
<td><strong>Sources for new drug safety information</strong>&lt;br&gt;• 89% of health professionals feel it is very important to stay current about new drug safety information, though fewer (56%) seek this type of information on a frequent basis.&lt;br&gt;• Unaided, 12% of health professionals listed Health Canada / MedEffect as a source for such information (2007, p. 2).&lt;br&gt;• 83% of health professionals report being very likely to read information received from Health Canada (2007, p. 3).**&lt;br&gt;<strong>ADRs</strong>&lt;br&gt;• About half the health professionals claim familiarity with how to report an adverse reaction; pharmacists were most likely to report being familiar with this process (87%), followed by physicians (51%). Overall, 37% of health professionals indicated they knew where to obtain an ADR reporting form (2007, p. 3).</td>
</tr>
<tr>
<td>(Follow-up to 2003 survey)</td>
<td></td>
<td>-------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>(Only executive summary is available online)</td>
<td></td>
<td>-------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>(Environics Research Group, 2007)</td>
<td></td>
<td>-------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Underutilization of the Adverse Reaction Reporting System</td>
<td>Health professionals (n=48)</td>
<td><strong>Sources for new drug safety information</strong>&lt;br&gt;• Mostly commonly, health professionals seek post-market drug information through the College of Physicians and Surgeons, journals, and interaction with colleagues.&lt;br&gt;• Very few health professionals were aware of the MedEffect website, and among those who were aware, only one had subscribed to the e-notice.&lt;br&gt;• Only three health professionals (two pharmacists and a medical doctor) indicated they had ever reported an ADR.&lt;br&gt;• There is a lack of awareness regarding how and why ADRs should be reported, and who should be making these reports to Health Canada.<strong>&lt;br&gt;<strong>Results of drug safety survey of Canadians</strong>&lt;br&gt;• A 2007 survey of an unidentified number of Canadians showed most Canadians were either somewhat concerned (29%) or concerned (48%) about the safety of medicines.&lt;br&gt;• The same survey showed that slightly fewer Canadians were either somewhat concerned (25%) or concerned (43%) about the safety of vaccines.&lt;br&gt;• A 2010 survey of 1,008 Canadians showed that about 65% feel medications approved by Health Canada are safe.</strong>&lt;br&gt;<strong>Canadians’ Awareness of Health and Safety Issues Related to Consumer Products</strong>&lt;br&gt;• Research was conducted on awareness of health and safety issues related to a wide range of consumer products, which included “medications.” However, the survey report does not describe results by product type, and, therefore, data from this survey could not be used.&lt;br&gt;• The survey examined topics such as sources of safety information; awareness and use of safety information such as advisories, warnings, and recalls; and subscription to Health Canada RSS feeds.</td>
</tr>
<tr>
<td>(Phoenix Strategic Perspectives Inc, 2011)</td>
<td>Public Focus groups (x8) (n=64)</td>
<td>-------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
## Table 9: Domestic GMP inspections for human drugs (including biologics) and veterinary drugs (2005–2006 to 2012–2013)

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Beginning backlog</th>
<th>Annual inspection target</th>
<th>Inspections</th>
<th>Complete to annual target</th>
<th>Non-compliant</th>
<th>Compliancy rate</th>
<th>Backlog to carry over</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005–06</td>
<td>N/A</td>
<td>567</td>
<td>420</td>
<td>74%</td>
<td>21</td>
<td>95%</td>
<td>165</td>
</tr>
<tr>
<td>2006–07</td>
<td>165</td>
<td>543</td>
<td>356</td>
<td>66%</td>
<td>6</td>
<td>98%</td>
<td>187</td>
</tr>
<tr>
<td>2007–08</td>
<td>190</td>
<td>484</td>
<td>446</td>
<td>92%</td>
<td>9</td>
<td>98%</td>
<td>170</td>
</tr>
<tr>
<td>2008–09</td>
<td>210</td>
<td>689</td>
<td>440</td>
<td>64%</td>
<td>8</td>
<td>98%</td>
<td>57</td>
</tr>
<tr>
<td>2009–10</td>
<td>117</td>
<td>475</td>
<td>406</td>
<td>86%</td>
<td>15</td>
<td>96%</td>
<td>N/A</td>
</tr>
<tr>
<td>2010–11</td>
<td>66</td>
<td>414</td>
<td>342</td>
<td>83%</td>
<td>14</td>
<td>96%</td>
<td>N/A</td>
</tr>
<tr>
<td>2011–12</td>
<td>35</td>
<td>472</td>
<td>423 (+39 withdrawn)</td>
<td>97.9%**</td>
<td>13</td>
<td>97%</td>
<td>N/A</td>
</tr>
<tr>
<td>2012–13</td>
<td>34</td>
<td>401</td>
<td>328 (+21 withdrawn)</td>
<td>90%**</td>
<td>21</td>
<td>96%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Source: (Inspectorate, 2007, 2010b) and data provided by Health Canada.
* This is presumed to refer to inspections initiated.
** Includes inspections that were removed from the plan due to establishment inactivity or other reasons for withdrawal.

## Table 10: Inspections of blood establishments (2003–2004 to 2012–2013)

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Beginning backlog</th>
<th>Target</th>
<th>Inspections completed</th>
<th>Completed to target</th>
<th>Non-compliant</th>
<th>Compliancy rate</th>
<th># to be completed</th>
<th>On-site evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003–04</td>
<td>-</td>
<td>-</td>
<td>21</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2005–06</td>
<td>0</td>
<td>19</td>
<td>19</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2006–07</td>
<td>N/A</td>
<td>21</td>
<td>21</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2007–08</td>
<td>0</td>
<td>25</td>
<td>25</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2008–09</td>
<td>0</td>
<td>34</td>
<td>34</td>
<td>103%</td>
<td>0</td>
<td>100%</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2009–10</td>
<td>0</td>
<td>33</td>
<td>34</td>
<td>103%</td>
<td>0</td>
<td>100%</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2010–11</td>
<td>0</td>
<td>27</td>
<td>29</td>
<td>107%</td>
<td>0</td>
<td>100%</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>2011–12</td>
<td>0</td>
<td>37</td>
<td>41</td>
<td>111%</td>
<td>0</td>
<td>100%</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>2012–13</td>
<td>0</td>
<td>32</td>
<td>30 (+2 withdrawn)</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td>0</td>
<td>2 (first time inspections)</td>
</tr>
</tbody>
</table>

Source: (Inspectorate, 2004b, 2007, 2010b) and data provided by Health Canada.

## Table 11: Inspections of cells, tissues, and organ establishments (2005–2006 to 2012–2013)

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Beginning backlog</th>
<th>Target</th>
<th>Inspections</th>
<th>Completed to target</th>
<th>Non-compliant</th>
<th>Compliancy rate</th>
<th># to be completed</th>
<th>On-site evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005–06</td>
<td>56</td>
<td>-</td>
<td>43</td>
<td>-</td>
<td>22 (quarantine action required)</td>
<td>-</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>2006–07</td>
<td>13</td>
<td>-</td>
<td>8</td>
<td>-</td>
<td>6 (quarantine action required)</td>
<td>-</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2007–08</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
<td>0</td>
<td>N/A</td>
<td>0</td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>2008–09</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
<td>0</td>
<td>N/A</td>
<td>0</td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>2009–10</td>
<td>0</td>
<td>34</td>
<td>24</td>
<td>71%</td>
<td>0</td>
<td>100%</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>2010–11</td>
<td>10</td>
<td>55</td>
<td>42 (+3 withdrawn)</td>
<td>76%</td>
<td>5</td>
<td>88%</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>2011–12</td>
<td>13</td>
<td>56</td>
<td>65 (+5 withdrawn)</td>
<td>125%</td>
<td>8</td>
<td>88%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2012–13</td>
<td>0</td>
<td>47</td>
<td>45 (+2 withdrawn)</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Source: (Inspectorate, 2007, 2008, 2010b) and data provided by Health Canada.
### Table 12: Inspections of semen establishments (2003–2004 to 2012–2013)

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Beginning backlog</th>
<th>Target</th>
<th>Inspections</th>
<th>Completed to target</th>
<th>Non-compliant</th>
<th>Compliancy rate</th>
<th>Ending backlog</th>
<th># inactive establishments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003–04</td>
<td>-</td>
<td>-</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2005–06</td>
<td>N/A</td>
<td>2</td>
<td>2</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td>N/A</td>
<td>-</td>
</tr>
<tr>
<td>2006–07</td>
<td>N/A</td>
<td>7</td>
<td>7</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2007–08</td>
<td>N/A</td>
<td>49</td>
<td>35</td>
<td>71%</td>
<td>0</td>
<td>100%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2008–09</td>
<td>0</td>
<td>53</td>
<td>45</td>
<td>85%</td>
<td>4</td>
<td>91%</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>2009–10</td>
<td>2</td>
<td>32</td>
<td>23</td>
<td>72%</td>
<td>0</td>
<td>100%</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>2010–11</td>
<td>0</td>
<td>34</td>
<td>35</td>
<td>103%</td>
<td>4</td>
<td>89%</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>2011–12</td>
<td>0</td>
<td>25</td>
<td>15 (+10 withdrawn)</td>
<td>100%</td>
<td>1</td>
<td>93%</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>2012–13</td>
<td>0</td>
<td>37</td>
<td>33 (+8 withdrawn)</td>
<td>111%</td>
<td>1</td>
<td>97%</td>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

Source: (Inspectorate, 2004b, 2007, 2009, 2010b) and data provided by Health Canada
<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Target</th>
<th>Inspections completed</th>
<th>Complete to annual target</th>
<th>Non-compliant</th>
<th>Compliancy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004–05</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>2005–06</td>
<td>243</td>
<td>75</td>
<td>31%</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>2006–07</td>
<td>256</td>
<td>120</td>
<td>47%</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>2007–08</td>
<td>242</td>
<td>153</td>
<td>63%</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>2008–09</td>
<td>94</td>
<td>76</td>
<td>81%</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>2009–10</td>
<td>64</td>
<td>72</td>
<td>113%</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>2010–11</td>
<td>97</td>
<td>86</td>
<td>89%</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>2011–12</td>
<td>107</td>
<td>100</td>
<td>94%</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>2012–13</td>
<td>81</td>
<td>82</td>
<td>101%</td>
<td>0</td>
<td>100%</td>
</tr>
</tbody>
</table>

Source: (Inspectorate, 2004a, 2006, 2007, 2010b) and data provided by Health Canada.

Changed to Good Pharmacovigilance Practices (GVP) in 2012–2013.

<table>
<thead>
<tr>
<th>Fiscal year</th>
<th>Personal shipments</th>
<th>Commercial shipments</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Refusal (Suspected)</td>
<td>Releases All other</td>
<td>Refusal (Suspected)</td>
</tr>
<tr>
<td>Biologics (Schedule C), Food and Drug Regulations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010–2011</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>2011–2012</td>
<td>17</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>2012–2013</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Biologics (Schedule D), Food and Drug Regulations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010–2011</td>
<td>1</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>2011–2012</td>
<td>17</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>2012–2013</td>
<td>54</td>
<td>3</td>
<td>12</td>
</tr>
</tbody>
</table>

Source: (Inspectorate, 2010a, 2011, 2012a) and data provided by Health Canada.
<table>
<thead>
<tr>
<th>Name</th>
<th>Description/mandate</th>
<th>Documented activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expert Advisory Committee on the Vigilance of Health Products (EAC-VHP)</td>
<td>The Committee’s mandate “is to provide HPFB with ongoing external expert broad strategic policy advice on the safety and therapeutic effectiveness of marketed health products for human use. It will also provide a mechanism to involve the public, providing them with a forum to have their views heard by experts who can discuss their input and incorporate it into the advice provided” (MHPD, 2006).</td>
<td>• There is record of nine meetings being held from 2007 to 2009 • The Committee engaged in discussion and provided advice on 47 presented topics. The Committee’s advice was used in developing the Recommendations for the Appropriate Use of Cough and Cold Products in Children document (MHPD, 2008). • The Committee developed a Public Involvement Plan. Of the 450 stakeholders who were invited to provide input on three questions, 58 contributed prior to the meeting and 16 did at the meeting.</td>
</tr>
<tr>
<td>Paediatric Expert Advisory Committee</td>
<td>The Committee, which was formed in 2009, has the objective “to provide a way for Health Canada to seek expert advice and public involvement in the development, licensing, and continued vigilance for health products — pharmaceuticals, medical devices, biologics including vaccines and natural health products — on the market destined for children, and pregnant and nursing women.” (Health Canada, 2012b) The Committee also provides input related to food safety and nutrition. It consists of 15 experts, including paediatric specialists, university professors, pharmacists, researchers, industry/patient groups, not-for-profit organizations, and parents (Health Canada, 2012b).</td>
<td>• In May 2010, the Committee discussed “off-label” use of drugs in the paediatric population. Documents suggest that this led to a “Mind the Gap” study initiated by the Office of Paediatric Initiatives to address issues related to off-label drug use in paediatrics (MHPD, 2011). • Sponsored an initiative to provide “an evidence-based and authoritative assessment on the state of therapeutic products for children in Canada and abroad” (GoC, 2012, p. 16:10)</td>
</tr>
<tr>
<td>Scientific Advisory Panel on Oncology Therapies (SAC-OT)</td>
<td>The Committee “provides Health Canada with timely scientific, technical, and medical advice related to the regulation of oncology therapies. Involvement of the scientific, medical and consumer communities in the regulatory review process is expected to enhance transparency and provide opportunity for proactive external guidance, thus facilitating the drug review process. The SAC-OT provides Health Canada with advice and recommendations, but the decision-making responsibility remains with Health Canada” (TPD, 2010b).</td>
<td>• There is record of four meetings taking place on September 13, 2007; February 26, 2009; April 15, 2010; and December 6, 2011. At these meeting the answers and recommendations on six topics posed to the Committee were provided (TPD, 2011b).</td>
</tr>
<tr>
<td>Scientific Advisory Committee on Respiratory and Allergy Therapies (SAC-RAT)</td>
<td>The Committee “will provide Health Canada with ongoing and timely scientific, technical, and medical advice on the evaluation of safety, efficacy, and effectiveness of drugs used for the treatment of respiratory diseases and allergic conditions as well as policy issues”(TPD, 2010c).</td>
<td>• There is record of eight meetings taking place since 2006 (TPD, 2012b). • The Committee has developed two draft documents which are yet to be finalized: Submission Requirements for Subsequent Market Entry Inhaled Corticosteroid Products for Use in the Treatment of Asthma; and Submission Requirements for Subsequent Market Entry Steroid Nasal Products for Use in the Treatment of Allergic Rhinitis (TPD, 2012b).</td>
</tr>
<tr>
<td>Expert Advisory Panel on the Special Access Programme (EAP-SAP)</td>
<td>The Panel “acts as a forum of advice and a sounding board for management and scientists of [HPFB]. Panel members … meet to discuss options for improving the regulatory framework under which the Special Access Programme will function” (Health Canada, 2007)</td>
<td>• Nothing regarding the Panel’s activity was available in the documents provided to the consultant. • According to Health Canada’s website, this Panel’s mandate has been completed (Health Canada, 2012d).</td>
</tr>
<tr>
<td>Scientific Advisory Committee on Human Reproductive Therapies (SAC-HRT)</td>
<td>The Committee “provides [HC] with timely scientific, technical and medical advice related to the evaluation of safety and efficacy data for human reproductive therapies that are submitted as part of the drug/medical devices review process and/or from post-market surveillance activities.” The Panel will “enhance transparency and provide the opportunity for proactive external guidance” (TPD, 2003).</td>
<td>• Nothing regarding the Panel’s activity was available in the documents provided to the consultant. • According to Health Canada’s website, this Panel’s mandate has been completed (Health Canada, 2012a).</td>
</tr>
<tr>
<td>Name</td>
<td>Description/mandate</td>
<td>Documented activity</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Scientific Advisory Committee on Metabolic and Endocrine Therapies</td>
<td>The Committee provides HC with “advice related to the evaluation of safety and efficacy data for metabolic and endocrine drug products that are submitted as part of the drug/medical device assessment process and/or from post-market surveillance activities. Involvement of [the Committee] in the regulatory review process is expected to enhance transparency and provide opportunity for proactive external guidance, thus facilitating the drug/medical device assessment process” (Health Canada, 2006)</td>
<td>• There is record of one meeting taking place on November 15, 2007(Health Canada, 2006)</td>
</tr>
<tr>
<td>SAC-MET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scientific Advisory Committee on Musculoskeletal Therapies (SAC-MST)</td>
<td>No information available.</td>
<td>• Committee was cancelled (Health Canada, 2011a)</td>
</tr>
<tr>
<td>Scientific Advisory Committee on Neurological Therapies (SAC-NT)</td>
<td>No information available.</td>
<td>• Committee was cancelled (Health Canada, 2011a)</td>
</tr>
</tbody>
</table>
| Expert Advisory Panel on Avastin                                    | The EAP on Avastin was convened by BGTD in 2011 to advise the Directorate on the benefit-risk analysis of Avastin (a humanized antibody) in the treatment of metastatic HER2-negative breast cancer and in combination with paclitaxel (a plant-derived drug) (BGTD, 2011b). The Panel was to conduct a single meeting to discuss and review information on the product and submit a report on its conclusions to BGTD. | • The Panel convened by teleconference on March 15, 2011, to discuss information on Avastin as provided by BGTD and the manufacturer, conduct a review of the data, and provide conclusions and recommendations on questions provided by BGTD (BGTD, 2011b).  
• The Panel submitted its conclusions in a report on April 29, indicating that Avastin suffered from fundamental problems of efficacy that made it unsuitable as a first-line or second-line therapy regardless of any potential product monograph (BGTD, 2011b).  
• In an advisory for Health Professionals on November 29, 2011, Health Canada informs them about a decision to suspend the NOC/c for Avastin in combination with paclitaxel for treatment of patients with metastatic breast cancer. The action does not impact Avastin’s approved uses for other cancer types. Avastin remains listed as Active in the Drug Product Database. |
| Expert Advisory Panel on Insulin                                     | The EAP on Insulin convened at the request of BGTD in 2008 to discuss insulin preparation issues around knowledge, availability, and labelling (BGTD, 2010e). BGTD provided multiple questions to the Panel on various subjects, including the use of animal insulin, clinical practice, research needs and gaps, side effects, adverse reactions, and the development of immunogenicity. | • The Panel met on October 30, 2008, and received presentations from BGTD, MHPD, the Insulin Dependent Diabetes Trust International, and the Canadian Diabetes Association. The Panel then discussed questions posed by BGTD on various insulin issues (BGTD, 2008).  
• The Panel produced a report with comments and 20 recommendations regarding each of BGTD’s questions, which was published with Health Canada’s responses to the Health Canada website (BGTD, 2010e). Some of the responses from Health Canada propose specific actions to respond to the recommendations.  
• There is some evidence Health Canada acted on these proposed actions with respect to communications. For example, Health Canada posted the Panel report on its website, created an It’s Your Health document on type 2 diabetes and weight gain from insulin (Health Canada, 2011b) and posted another It’s Your Health document on insulin products which contains a Panel-recommended statement on hypoglycaemia unawareness (Health Canada, 2010). |
| Expert Advisory Panel on Avastin                                    | The EAP on Avastin was convened by BGTD in 2011 to advise the Directorate on the benefit-risk analysis of Avastin (a humanized antibody) in the treatment of metastatic HER2-negative breast cancer and in combination with paclitaxel (a plant-derived drug) (BGTD, 2011b). The Panel was to conduct a single meeting to discuss and review information on the product and submit a report on its conclusions to BGTD. | • The Panel convened by teleconference on March 15, 2011, to discuss information on Avastin as provided by BGTD and the manufacturer, conduct a review of the data, and provide conclusions and recommendations on questions provided by BGTD (BGTD, 2011b).  
• The Panel submitted its conclusions in a report on April 29, indicating that Avastin suffered from fundamental problems of efficacy that made it unsuitable as a first-line or second-line therapy regardless of any potential product monograph (BGTD, 2011b).  
• In an advisory for Health Professionals on November 29, 2011, Health Canada informs them about a decision to suspend the NOC/c for Avastin in combination with paclitaxel for treatment of patients with metastatic breast cancer. The action does not impact Avastin’s approved uses for other cancer types. Avastin remains listed as Active in the Drug Product Database. |
<table>
<thead>
<tr>
<th>Name</th>
<th>Description/mandate</th>
<th>Documented activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Expert Advisory Panel on Prochymal</strong></td>
<td>The EAP on Prochymal was convened by BGTD in 2012 to advise the Directorate on the benefits and risks of a new mesenchymal stem cell therapy called Prochymal (BGTD, 2012b). Prochymal had been submitted as an NDS and, after a priority review (including review by the Panel), was given a Notice of Compliance with Conditions.</td>
<td><strong>•</strong> The panel reviewed materials prior to convening for a full day meeting in Ottawa on January 26, 2012, where they discussed Health Canada’s assessments and industry presentations on clinical trial information (BGTD, 2012b). The Panel then provided advice and recommendations to BGTD based on a set of predefined questions regarding adequacy of data, safety and risks, and considerations for appropriate labelling and use of the therapy. The recommendations related to adequacy of data to evaluate efficacy of Prochymal, appropriate treatment timing and age ranges in the paediatric population, dosage and administration, long-term effects, labelling, and other safety considerations (BGTD, 2012b). The final regulatory decision was left to BGTD. <strong>•</strong> The Panel’s recommendations were included as conditions for the manufacturer to meet as part of the Notice of Compliance with Conditions (Health Canada, 2012c).</td>
</tr>
<tr>
<td><strong>Expert Advisory Committee on Blood Regulation</strong></td>
<td>The EAC on Blood Regulation advises BGTD in issues of risk management in the national blood system, including but not limited to whole blood, blood components, and blood products. The Committee provides expertise from the perspective of health professionals and related areas (BGTD, 2012a).</td>
<td><strong>•</strong> Documents were available regarding six face-to-face meetings, covering Committee activities from April 2008 to September 2012. <strong>•</strong> The Committee annually provided opinions and advice based on the PHAC surveillance reports for HIV and AIDS in Canada (BGTD, 2009c, 2010d). <strong>•</strong> The Committee also provided advice to Health Canada on the development of CTO Surveillance (BGTD, 2009d). <strong>•</strong> Following an extensive discussion of plasma provision issues, a Committee representative contacted Canadian Blood Services and Héma-Quebec to determine safety procedures around specific blood products (BGTD, 2009d). <strong>•</strong> The Committee discussed and supported the use of a new staffing model within CBS (BGTD, 2010c). <strong>•</strong> In 2010, a joint meeting of the CTO and Blood Regulation EACs was held (BGTD, 2010c). Both Committees agreed to continue to not recommend changes to CTO donor screening criteria, but recommended specific types of data to be collected in order to meaningfully revisit the issue in future. <strong>•</strong> The Committee provided responses and advice to Health Canada on risk management strategies for the emerging leukemia-related XMRV infection and requested ongoing updates on the situation (BGTD, 2010d, 2011a).</td>
</tr>
<tr>
<td><strong>Expert Advisory Committee on Cells, Tissues, and Organs</strong></td>
<td>The EAC on Cells, Tissues, and Organs advises BGTD on issues related to the safety, quality, and efficacy of cells, tissues, and organs intended for use as transplants (Health Canada, 2012d). The Committee’s expertise includes but is not limited to health professionals, and may be relevant to risk/benefit assessments and other risk management activities.</td>
<td><strong>•</strong> The inaugural meeting of the EAC-CTO took place September 15, 2005. Documents were available regarding three face-to-face meetings and four teleconferences, covering Committee activities from May 2008 to February 2012. <strong>•</strong> Following several meetings reviewing issues and input regarding the CTO Regulations, the Committee was to provide Health Canada with a report on recommended amendments to the CTO Regulations in 2009 (BGTD, 2009a). <strong>•</strong> The Committee finalized the Guidance Document for CTO establishments in June 2009 with a series of recommended changes and clarifications, and advised on the development of a CTO Surveillance framework (BGTD, 2009b). <strong>•</strong> In 2010, a joint meeting of the CTO and Blood Regulation Committees was held (BGTD, 2010b). The Committees both agreed to continue to not recommend changes to CTO donor screening criteria, but recommended specific types of data to be collected in order to meaningfully revisit the issue in future.</td>
</tr>
<tr>
<td>Signal Assessment Activities</td>
<td>Timelines</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------------------</td>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td>Number of signal assessments completed</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>Signal receipt to signal assignment, median working days</td>
<td>14 days</td>
<td></td>
</tr>
<tr>
<td>Signal receipt to signal assignment, mean working days</td>
<td>70 days</td>
<td></td>
</tr>
<tr>
<td>Completed within 130 working days, pre-April 2007</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Completed within 130 working days, post-April 2007</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>Low priority assessments meeting target of 200 working days, post-April 2007</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>Medium priority assessments meeting target of 130 working days, post-April 2007</td>
<td>99%</td>
<td></td>
</tr>
<tr>
<td>High priority assessments meeting target of 80 working days, post-April 2007</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Median processing time in working days, pre-April 2007</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Median processing time in working days, post-April 2007</td>
<td>46 days</td>
<td></td>
</tr>
<tr>
<td>Mean processing time in working days, pre-April 2007</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Mean processing time in working days, post-April 2007</td>
<td>70 days</td>
<td></td>
</tr>
</tbody>
</table>
### Table 17: HPFB participation in international fora and activities

<table>
<thead>
<tr>
<th>Activity/forum</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>American Association of Tissue Banks</strong></td>
<td>This group publishes standards, accredits tissue banks internationally, interacts with regulatory agencies, and conducts educational meetings and training. BGTD is a member of the Standards Committee responsible for standard development, including 13th edition of the American Association of Tissue Banks (AATB) standards, which was published in March 2012.</td>
</tr>
<tr>
<td><strong>Asia Pacific Economic Cooperation (APEC) through the Regulatory Harmonization Steering Committee (RHSC)</strong></td>
<td>TPD chairs the RHSC, the mandate of which is to promote harmonization and identify projects of highest value in partnership with the APEC Harmonization Center, other harmonization initiatives, training organizations, and international players such as the WHO. In 2011, the APEC ministers endorsed the Strategic Framework on Regulatory Convergence of Medical Products by 2020. Health Canada currently chairs APEC’s Life Sciences Working Group.</td>
</tr>
<tr>
<td><strong>APEC GCP Inspector’s Working Group</strong></td>
<td>The Inspectorate participates in this group, which promotes harmonization of GCP and provides opportunities for networking and sharing of best practices with international colleagues. The group also supports development of regulatory frameworks of countries with less-developed regulatory systems.</td>
</tr>
<tr>
<td><strong>African Medicines Registration Harmonization (AMRH)</strong></td>
<td>Assists African countries to harmonize medicines registration, and reduce the time spent to register priority essential medicines. AMRH partners assist Regional Economic Communities in Africa in their development of project proposals for medicines registration harmonization projects. The kick-off stakeholders meeting was scheduled for March 28, 2012, in Tanzania.</td>
</tr>
<tr>
<td><strong>Canadian HIV Vaccine Initiative (CHVI)</strong></td>
<td>This is a five-year collaborative initiative between the Government of Canada and the Bill &amp; Melinda Gates Foundation. Through this initiative, BGTD provides training to emerging national regulatory authorities (NRAs) from low- and middle-income countries to strengthen regulatory frameworks in relation to clinical trials and market authorization for vaccines. The initiatives below are supported through the CHVI.</td>
</tr>
<tr>
<td>a. <strong>African Vaccines Regulatory Forum</strong></td>
<td>BGTD participates in this group, which provides regulators with expert advice on the evaluation of vaccines. The forum helps decision making with respect to clinical trial authorization, evaluation of registration dossiers, or other issues in vaccine evaluation.</td>
</tr>
<tr>
<td>b. <strong>CVHI Regulatory Capacity Building Mentorship Program</strong></td>
<td>This mentorship program is intended to provide one-on-one learning opportunities for NRAs to strengthen regulatory capacity in biologics and vaccines. BGTD initiated a mentorship program with Malawi in 2012 under the Program.</td>
</tr>
<tr>
<td>c. <strong>Developing Countries’ Vaccine Regulators Network</strong></td>
<td>BGTD participates in this network, which promotes regulatory capacity development of NRAs through expertise and exchange of information about evaluation of clinical trial proposals and clinical trial data.</td>
</tr>
<tr>
<td>d. <strong>Second International Congress on Pharmacology of Vaccines</strong></td>
<td>BGTD participated with PAHO countries in this congress (VacciPharma 2012) to discuss the use of prophylactic vaccines in relation to HIV.</td>
</tr>
<tr>
<td><strong>Heads of Agencies Consortium</strong></td>
<td>The Heads of Agencies Consortium also includes the TGA, Swissmedic, and Singapore’s Health Sciences Authority with the goal of leveraging expertise and knowledge and identifying work-sharing opportunities. The group has developed a plan of action on generic drugs and has created a standardized template and process for sharing applications in queue and identifying common applications. Efforts are also currently underway for the partner agencies to work together in the review of PSURs.</td>
</tr>
<tr>
<td><strong>International Laboratory Forum on Counterfeit Medicines (ILFCM)</strong></td>
<td>Health Canada participates in the ILFCM, which is an informal information sharing forum for experts to share experiences about important operational issues such as the interception and analysis of counterfeit therapeutic products. The forum meets semi-annually.</td>
</tr>
<tr>
<td><strong>International Generic Drug Regulators’ Group (IGDRG)</strong></td>
<td>Health Canada participates in the IGDRG, which is a forum for regulatory authorities to explore collaborative opportunities in the area of generic drugs. Collaborative opportunities include work sharing and increased regulatory alignment. At least two face-to-face meetings have taken place, resulting in a consensus on goals, objectives, and priority areas for collaboration.</td>
</tr>
<tr>
<td><strong>International Regulatory Forum</strong></td>
<td>An annual forum that is intended to contribute to African and Asian development and collaboration within the Americas. The fourth annual International Regulatory Forum was planned for September 24–28, 2012, in Ottawa, with approximately 100 participants from over 40 countries</td>
</tr>
<tr>
<td><strong>OMCL Network</strong></td>
<td>The Inspectorate Laboratories participate in this network. Annual meetings permit exchange on best practices and topics of interest among managers of medicines control laboratory in Europe, Australia, and Canada.</td>
</tr>
<tr>
<td>Activity/forum</td>
<td>Description</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Pan American Health Organization (PAHO)</strong></td>
<td>PAHO has requested that the HPFB undergo a WHO/PAHO regulatory assessment as part of the PAHO Directing Council resolution on strengthening National Regulatory Authorities. This would allow Health Canada to serve as a model for other authorities within the hemisphere and improve its own regulatory programs (BGTD’s vaccines program has already been qualified).</td>
</tr>
<tr>
<td><strong>Pan American Network for Drug Regulatory Harmonization (PANDRH) Cooperation</strong></td>
<td>This network supports the processes of pharmaceutical regulatory harmonization in the Americas. TPD participates on the Steering Committee and BGTD participates in two PANDRH working groups (biotechnological products and vaccines), which have produced international guidance on these topics.</td>
</tr>
</tbody>
</table>
| **Pharmaceutical Inspection Cooperation Scheme (PIC/S) and PIC/S-MRA Special collaboration** | PIC/S has multiple objectives, including:   
- facilitate the networking and cooperation between participating Regulatory Authorities;  
- maintain mutual confidence;  
- promote quality assurance of inspections;  
- exchange information and experience in the field of GMP and related areas;  
- coordinate mutual training of GMP inspectors; and  
- improve and harmonize technical standards and procedures related to GMP with a view to contributing to global harmonization.  
   HPFB participates in various PIC/S working groups. Health Canada is also currently involved in a special collaboration to assess the feasibility of a closer collaboration with the Pharmaceutical Inspection Convention/Scheme (PIC/S) in a joint evaluation program for countries that want to join the MRA program and PIC/Ss. This fiscal year, some PIC/Ss representatives are working with one MRA Officer with the VMD authority as a pilot assessment of this eventual collaboration. The team of evaluators is composed of the Czech Republic as a lead, as well as Switzerland and Health Canada. |
| **International Organization for Standardization**                          | HPFB participated in the development of ISO – TC215, the purpose of which is to enable open and free sharing of international safety data, promote interoperability between independent systems, and enable compatibility and consistency for health information and data. MHPD participates in the TC215, Health Informatics Working Group 6 – Pharmacy and medicines business. |
| **Four-way pharmacovigilance teleconference**                              | HPFB participates in a four-way pharmacovigilance teleconference, which began in 1998 and consists of the MHPD/HPFB, Centre for Drug Evaluation and Research/FDA, Adverse Drug Reaction Unit/TGA, Medsafe/New Zealand, and Health Sciences Authority/Singapore. The teleconference acts as a forum for exchange and discussion of health product vigilance and promotes coordination of pharmacovigilance efforts between jurisdictions by creating awareness of emerging safety issues in each regulatory authority. The meeting is held every two months, with the chair rotating between agencies. |
| **Cooperation with WHO on biological standardization and evaluation of biologics** | BGTD cooperated with the WHO on biological standardization and evolution of biologics, including work in key areas of vaccines, and HIV/AIDS vaccines. Activities include provision of technical advice and assistance in to develop biologic regulatory standards, provision of assistance to the WHO pre-qualification program, and implementation of WHO guidelines into regulatory practice. |
| **WHO International Drug Monitoring Programme**                            | Intended to enhance collaboration between regulatory agencies through discussion and information sharing. The Forums allow Health Canada to share its pharmacovigilance expertise to help countries developing pharmacovigilance programs. As part of their participation in the Forum, Health Canada uploads adverse reaction reports into the WHO Vigibase database. |
| **WHO CIOMS**                                                               | CIOMS aims at improving the methodology and the standardisation in the field of biomedical science (i.e., risk minimization). The reports produced by CIOMS have become the basis of several international guidance documents related to health product review and surveillance. MHPD participates in several working groups. |
| **WHO Pre-Qualification Programme for Pharmaceuticals**                     | This program assesses pharmaceutical applications submitted to the WHO’s expressions of interest. These assessments ensure the quality of medicines procured by UN funding agencies to be sent to eligible countries, and contribute to the UN’s goal of addressing widespread diseases in countries with limited access to quality medicines. Up to six review sessions are conducted each year. |
| **International Medical Products Anti-Counterfeiting Task Force (IMPACT)**   | IMPACT works to determine appropriate actions to take in response to the availability of compromised medical products. |
| **ExL Pharma Conference on Proactive GCP Compliance**                       | This three-day conference in Arlington, Virginia provided an opportunity to educate international stakeholders about Canadian regulatory requirements for clinical trials and network with international regulators. |
Recall data

To derive the data on product recalls, the consultant compiled information on recalls from the online Drug Recall Listing. The analysis included data up to and including August 23, 2012. A table listing all of the recalls identified in this way was circulated to TPD and BGTD with a request to identify those pertaining to human pharmaceutical drugs and biologics, respectively. The analysis excluded 181 of the originally identified recalls for the following reasons: 106 recalls involved products that the TPD could not identify, often because the listing had no market authorization number; 40 recalls involved natural health products that contain pharmaceutical ingredients; and 35 recalls involved products that could not be definitively identified by the TPD as either a pharmaceutical or a natural health product. A total of 666 recall notices for pharmaceutical drugs and biologics (31 notices) were included in the analysis. Given the steps involved in completing this analysis, the analysis was not updated to include the entire 2012 year.

<table>
<thead>
<tr>
<th>Year</th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Other/unspecified**</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Biol.</td>
<td>Pharm</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>11</td>
<td>11</td>
<td>0</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>2006</td>
<td>11</td>
<td>11</td>
<td>10</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>2007</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>2008</td>
<td>13</td>
<td>13</td>
<td>5</td>
<td>8</td>
<td>36</td>
</tr>
<tr>
<td>2009</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>1</td>
<td>56</td>
</tr>
<tr>
<td>2010</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>57</td>
</tr>
<tr>
<td>2011</td>
<td>17</td>
<td>17</td>
<td>4</td>
<td>6</td>
<td>48</td>
</tr>
<tr>
<td>2012</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>51</td>
</tr>
<tr>
<td>Unspecified</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>6</td>
<td>65</td>
<td>18</td>
<td>337</td>
</tr>
</tbody>
</table>


Notes: Table excludes the following cases: 106 recalls involving products that the TPD could not identify, often because the listing had no market authorization number; 40 recalls involving NHPs that contain pharmaceutical ingredients; and 35 recalls involving products that could not be definitively identified by the TPD as a pharmaceutical or NHP.

* A recall is included in a given year if the recall start date occurs in that year

** This field includes cases that were categorized by the Inspectorate as: N/A, Unacceptable Risk to Health, a market withdrawal order from Health Canada, or were blank.

<table>
<thead>
<tr>
<th>Year</th>
<th>Not serious</th>
<th>Serious</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>%</td>
</tr>
<tr>
<td>1999</td>
<td>2,628</td>
<td>47.0%</td>
</tr>
<tr>
<td>2000</td>
<td>3,251</td>
<td>45.7%</td>
</tr>
<tr>
<td>2001</td>
<td>1,976</td>
<td>27.2%</td>
</tr>
<tr>
<td>2002</td>
<td>2,561</td>
<td>30.5%</td>
</tr>
<tr>
<td>2003</td>
<td>2,605</td>
<td>29.0%</td>
</tr>
<tr>
<td>2004</td>
<td>3,184</td>
<td>31.6%</td>
</tr>
<tr>
<td>2005</td>
<td>3,134</td>
<td>30.5%</td>
</tr>
<tr>
<td>2006</td>
<td>3,454</td>
<td>33.0%</td>
</tr>
<tr>
<td>2007</td>
<td>4,169</td>
<td>33.6%</td>
</tr>
</tbody>
</table>
Table 19: Serious adverse reaction reports as a proportion of all reports (public dataset, 1999–2012)

<table>
<thead>
<tr>
<th>Year</th>
<th>Not serious</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>#</td>
<td>%</td>
<td>#</td>
<td>%</td>
<td>#</td>
<td>%</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>4,918</td>
<td>31.6%</td>
<td>10,646</td>
<td>68.4%</td>
<td>15,564</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>5,210</td>
<td>28.0%</td>
<td>13,414</td>
<td>72.0%</td>
<td>18,624</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>6,604</td>
<td>29.7%</td>
<td>15,631</td>
<td>70.3%</td>
<td>22,235</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>8,064</td>
<td>28.1%</td>
<td>20,595</td>
<td>71.9%</td>
<td>28,659</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>2,286</td>
<td>26.6%</td>
<td>6,313</td>
<td>73.4%</td>
<td>8,599</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>54,044</td>
<td>31.0%</td>
<td>120,218</td>
<td>69.0%</td>
<td>174,262</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: (MHPD, 2012a)
Data for 2012 are current to June 30, 2012.
Table 20: Drugs inactivated by manufacturer for safety

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Active ingredient</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anzemet/Anzemet Injection</td>
<td>Dolestron mesylate</td>
<td>F</td>
</tr>
<tr>
<td>Apo-Phenylbutazone</td>
<td>Phenylbutazone</td>
<td>F</td>
</tr>
<tr>
<td>Apo-Thioridazine/Dom Thioridazine/Novo-Rizadine/PMS-Thioridazine/Thioridazine</td>
<td>Thioridazine hydrochloride</td>
<td>F</td>
</tr>
<tr>
<td>Apo-Sibutramine/Meridia</td>
<td>Sibutramine hydrochloride</td>
<td>F</td>
</tr>
<tr>
<td>PCI Pravastatin/Riva-Pravastatin</td>
<td>Pravastatin sodium</td>
<td>F</td>
</tr>
<tr>
<td>Bextra</td>
<td>Valdecoxin</td>
<td>F</td>
</tr>
<tr>
<td>Climacteron Injection</td>
<td>Estradiol benzoate, estradiol dienanthate, testosterone enanthate</td>
<td>G (CDSA IV)</td>
</tr>
<tr>
<td>Darvon-N</td>
<td>Destropropoxyphene</td>
<td>Narcotic (CDSA I)</td>
</tr>
<tr>
<td>Depakene</td>
<td>Valproic acid</td>
<td>F</td>
</tr>
<tr>
<td>Fluotic</td>
<td>Sodium fluoride</td>
<td>F</td>
</tr>
<tr>
<td>Fucidin</td>
<td>Fusidate sodium</td>
<td>F</td>
</tr>
<tr>
<td>Levo-T</td>
<td>Levothyroxine sodium</td>
<td>F</td>
</tr>
<tr>
<td>Palladone XL</td>
<td>Hydromorphone hydrochloride</td>
<td>Narcotic (CDSA I)</td>
</tr>
<tr>
<td>Permax/Shire-Pergolide</td>
<td>Pergolide mesylate</td>
<td>F</td>
</tr>
<tr>
<td>Prexige</td>
<td>Lumiracoxib</td>
<td>F</td>
</tr>
<tr>
<td>Raptiva</td>
<td>Efalizumab</td>
<td>D, F</td>
</tr>
<tr>
<td>Thelin</td>
<td>Sitaxsetan sodium</td>
<td>F</td>
</tr>
<tr>
<td>Vioxx</td>
<td>Rofecoxib</td>
<td>F</td>
</tr>
<tr>
<td>Xigris</td>
<td>Drotrecogin Alfa</td>
<td>D, F</td>
</tr>
<tr>
<td>Zelnorm</td>
<td>Tegaserod maleaste</td>
<td>F</td>
</tr>
</tbody>
</table>

Source: (Health Canada, 2013)

List of References for the Appendix C – Supplementary Data Tables


Health Canada. (2011c). Performance measurement and evaluation plan for the proposed fees in respect of Human Drugs and Medical Devices Regulations (version 8).


