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***CLINICAL TRIALS REGULATORY REVIEW: TARGETED MEASURES FOR  
A STRENGTHENED FRAMEWORK***

**Health Products and Food Branch  
Health Canada**

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## **1 Executive Summary**

On September 1, 2001, the regulatory amendments to Part C, Division 5 of the *Food and Drug Regulations* (Drugs for Clinical Trials Involving Human Subjects) came into force, with two overarching objectives:

- to strengthen protections for clinical trial subjects; and
- to attract and sustain investment in research and development in Canada.

Health Canada initiated a review of the clinical trials regulatory framework in 2006 with stakeholder consultations in the summer of 2006 and spring of 2007 to inform the development of measures to improve the clinical trials regulatory framework. Also, in the spring of 2007 Health Canada held a symposium entitled, *Context Matters: Gender Diversity and Clinical Trials*.

Health Canada officials have assessed the input received from stakeholders, considered best practices in other countries, as well as Health Canada's experience with the existing regulatory framework. The *Clinical Trials Regulatory Review: Targeted Measures for a Strengthened Framework* outlines a series of initiatives that Health Canada will undertake to further support the objectives of strengthening the protection of clinical trial subjects, and attracting and sustaining investments in research and development in Canada.

The review of the regulatory framework for clinical trials was undertaken in response to the commitment made to assess the impact of the new regulations within three to five years in Regulatory Impact Analysis Statement (RIAS) that accompanied the 2001 regulatory amendments. The review was also undertaken in the context of HPFB's *Blueprint for Renewal*, which aims to modernize the regulatory system for health products and food and is in-line with the Progressive Licensing Project and the review of the Special Access Programme, two other important deliverables under the *Blueprint* which will impact on the clinical trials regulatory framework in the longer-term.

### **Targeted Measures**

#### **Guidance to industry to assist in meeting regulatory obligations - Spring/Summer 2008**

Predictability is a critical element of a clinical trial sponsor's planning. Guidance documents provide assistance to sponsors on compliance with governing statutes and regulations and assistance to Health Canada staff on fair, consistent and effective implementation.

During consultations, stakeholders noted the need for better guidance on processes, requirements, roles and responsibilities in clinical trial activities. Stakeholders called for clear and consistent definitions and guidance on the requirements for various types of clinical trials.

Health Canada will proceed with revisions to current guidances and prepare new guidances as required on issues related to records retention, application and notification requirements, labelling, quality issues, good clinical practices, and the inclusion of women in clinical trials. Health Canada will also consider the possibility of regulatory amendments for a risk-based approach to records retention requirements.

### **Building on current processes for a more effective regulatory framework - Summer 2008**

Over the course of the review, a number of measures were identified to improve the efficiency and effectiveness of processes and to strengthen the infrastructure supporting the regulatory framework for clinical trials. In addition to the initiatives outlined below, Health Canada will also look to facilitate the submission of clinical trial applications (CTAs) such as electronic receipt and approval of CTAs and a secure e-mail communications system with clinical trials sponsors over the long-term.

Consistent with *Advantage Canada's* initiative to reduce red tape for businesses, Health Canada will proceed with modifications to the requirements for clinical trial application amendments (CTA-As), and will work towards expanding the application of the Canada Vigilance system to clinical trials for as streamlined reporting mechanism for adverse events.

Health Canada will also work towards enhancing the consistency and quality of REB reviews, which play a key role in clinical trials oversight and safety, through two key initiatives: the Sponsors' Table for Human Research Participant Protection and the development of a voluntary standard for REBs reviewing clinical trial applications.

### **Improving access to clinical trial information - Summer/Fall 2008**

Improving access to information about clinical trials to help patients and health providers make informed health decisions supports the Health Products and Food Branch's goal of providing Canadians with access to safe and effective health products and the information they need to make healthy choices. In support of this goal in the clinical trials area, Health Canada will launch a Canadian approach for the registration and disclosure of clinical trials in Canada.

Further consultations will be held as appropriate to assess the implications of these initiatives on the clinical trials environment in Canada. To achieve policy coherence across the Department, the various initiatives are being jointly carried out by clinical and policy staff within the Biologics and Genetic Therapies Directorate, the Inspectorate, the Marketed Health Products Directorate, the Policy, Planning and International Affairs Directorate, the Therapeutic Products Directorate, and the Health Policy Branch.

## Future trends

Consistent with the Government of Canada's commitment to a performance-based regulatory system that continually monitors and explores options for continuous improvement and in addition to the initiatives outlined in this plan, Health Canada will monitor and assess the implications of trends in the domestic and international clinical trials environment and continually adapt its framework to meet its objectives.

As Health Canada progresses with implementation of the initiatives listed above to strengthen and improve the regulatory framework for clinical trials, it will undertake focussed consultations with stakeholders, provinces and territories. Particular outreach efforts will be explored to ensure that the growing range of players involved in the clinical trials environment are given the opportunity to contribute to this strengthened framework. Stakeholders will also continue to have the opportunity to contribute to ongoing consultations on the Progressive Licensing Framework.

## 2 Introduction

On September 1, 2001, the regulatory amendments to Part C, Division 5 of the *Food and Drugs Regulations* (Drugs for Clinical Trials Involving Human Subjects) came into force, with two overarching objectives:

- to strengthen protections for clinical trial subjects; and
- to attract and sustain investment in research and development in Canada.

In the Regulatory Impact Analysis Statement (RIAS) that accompanied the 2001 regulatory amendments, Health Canada's committed to assessing the impact of the new regulations within three to five years. A review of the clinical trials regulatory framework was initiated in 2006. An issue identification paper was produced in March 2006, followed by an e-consultation in the summer of 2006 and a workshop in the spring 2007 seeking feedback from stakeholders on the 2001 framework and informing the development of measures to improve the clinical trials regulatory framework. To further inform this work, Health Canada held a spring 2007 symposium entitled, *Context Matters: Gender Diversity and Clinical Trials*.

Over the course of the summer 2007, Health Canada officials reviewed the feedback received by stakeholders and identified a number of initiatives to support the objectives of strengthening the protection of clinical trial subjects, and attracting and sustaining investments in research and development. *Clinical Trials Regulatory Review: Targeted Measures for a Strengthened Framework* is a plan which outlines those initiatives with consultations to be undertaken as they move forward.

### **3 The Life-cycle Approach to Regulating Health Products**

The *Blueprint for Renewal: Modernizing Canada's Regulatory System for Health Products and Food* was launched in October 2006, followed by national consultations with over 150 stakeholders. Strong support was expressed during these consultations for the approaches outlined in the *Blueprint* which highlighted a number of gaps in the regulatory system.

On December 17, 2007, the Prime Minister announced the *Food and Consumer Safety Action Plan* which will fundamentally change the regulatory system so that it can successfully respond to rapid changes in the regulatory environment and better protect the health and safety of Canadians. This shift will be achieved through the implementation of a life-cycle approach to regulating health products, an approach that is already being implemented by other leading regulators, such as the US Food and Drug Administration and the European Medicines Agency.

Core to the implementation of the life-cycle approach will be Health Canada's work with stakeholders in the drug development at the pre-clinical and clinical trial stages. This plan identifies initiatives to strengthen even further Health Canada's current oversight mechanisms and other aspects of the regulatory framework for clinical trials. In addition, a number of other initiatives, such as those pursued under the Progressive Licensing Project will ensure the implementation of Health Canada's life-cycle approach to regulating health products.

The objective of the Progressive Licensing Project is to create a modern regulatory framework for therapeutic products, including pharmaceuticals and biologics, that will provide oversight throughout the product lifecycle. A lifecycle approach to regulation will support the assessment of the risks and benefits of products throughout their entire life-cycle, both before and after they reach the market.

Although the essential information about a product's safety efficacy and quality is known at the time of marketing, the clinical trial process is limited in its abilities to detect rare adverse events, or test the product in every potential user. These limitations mean that the ongoing collection and analysis of information after a product is marketed is critical. As a result of marketing, many more people will be exposed to the product, and new information about how the product works in different people can be determined. Because the information about products increases over time, our understanding of its benefits and risks can change. Progressive Licensing means that Health Canada would assess the benefits and risks of a product before and after it reaches the market, establishing a stable regulatory standard that reflects a lifecycle approach to product regulation.

#### 4 Overview of Stakeholder Feedback - *What We Heard*

Health Canada launched an e-consultation in June 2006 with two primary objectives: to receive input from the public and stakeholder community on the impact and effectiveness of the 2001 clinical trials regulatory amendments, and to seek advice to improve the clinical trial framework design and implementation for the future.

The e-consultation resulted in a total of 73 submissions representing views from a range of stakeholders. Health Canada held a stakeholder workshop in the spring of 2007 with 48 participants representing industry, government, academia and non-governmental organizations to continue the dialogue with stakeholders on ways to improve the clinical trial regulatory framework for the future.

Most respondents indicated that the 2001 regulatory framework had met its objectives of strengthening protection for clinical trial subjects, and attracting and sustaining investment in research and development in Canada, and that these objectives continue to be relevant. However, additional flexibility is required to address emerging trends such as adaptive clinical trial designs, pharmacogenomics and to address the needs of specific populations.

A number of suggestions were offered to improve the regulatory framework:

- Development of relevant and timely guidances;
- Harmonization with global partners and other regulators;
- Flexibility to adapt to emerging needs such as sub-populations, genomics, adaptive clinical trials design, and scientific breakthroughs;
- Strengthened capacity for review and inspection;
- Transparency and consistent interpretation and application of the regulations;
- Predictability of processes; and
- Development of an accreditation system for human research protection.

Health Canada's spring 2007 symposium *Context Matters: Gender, Diversity and Clinical Trials* brought together 60 participants from across government and academia with a wide range of expertise in research methods, ethics, regulation and policy in relation to clinical trials. The goal was to identify and explore some of the challenges in moving from the controlled setting of clinical trials to real world use of health products. Among the issues raised:

- The need for clarity about when and why the inclusion of particular subgroups is necessary in clinical trials;
- Beyond inclusion, the need to address questions of sub-group analysis (e.g. by sex/gender, age, ethnicity), and statistical power;
- Attention to meaningful health outcomes and endpoints such as quality of life in clinical trials;

- Ethical issues, such as informed consent/assent in vulnerable populations such as children and seniors; and
- Attention to community participation, governance and need for culturally-sensitive health research in Aboriginal communities.

These issues will also help to inform the Progressive Licensing Project, the review of guidance documents and the understanding of emerging trends such as personalized approaches to treatment and disease prevention and are consistent with Health Canada's commitment to apply gender-based analysis to programs and policies in the areas of health system modernization, population health, risk management, and direct services and research.

Consultation reports are available on the [Clinical Trials Regulatory Review](#) section of the Health Canada website.

## **5 Targeted Measures**

Health Canada officials assessed the input received from stakeholders, considered best practices in other countries, as well as Health Canada experience with the existing regulatory framework. As a result, Health Canada will proceed with a series of initiatives to strengthen and improve the current regulatory framework for clinical trials.

- **Guidance to industry to assist in meeting regulatory obligations - Spring/Summer 2008**
- **Building on current processes for a more efficient and effective regulatory framework - Summer 2008**
- **Improving access to clinical trial information - Summer/Fall 2008**

Further consultations will be held as appropriate to assess the implications of the planned initiatives for the clinical trials environment in Canada. To achieve policy coherence across the Department, the various initiatives are being jointly carried out by clinical and policy staff within the Biologics and Genetic Therapies Directorate, the Inspectorate, the Marketed Health Products Directorate, the Policy, Planning and International Affairs Directorate, the Therapeutic Products Directorate, and the Health Policy Branch.

## **6 Guidance to Industry to Assist in Meeting Regulatory Obligations - Spring/Summer 2008**

Predictability is a critical element of a clinical trial sponsor's planning. Guidance documents provide assistance to sponsors on compliance with governing statutes and regulations and assistance to Health Canada staff on fair, consistent and effective implementation.



During consultations, stakeholders noted the need for better guidance on processes, requirements, roles and responsibilities in clinical trial activities. Stakeholders called for clear and consistent definitions and guidance on the requirements for various types of clinical trials. Other recommendations included the creation of frequently-asked questions and a glossary of terms at the back of all documents. Health Canada identified a number of topics on which it will proceed with developing and improving guidance.

The following principles will apply to the review of the guidances:

- The protection of clinical trial subjects will continue to be the primary consideration;
- Provision of clear information and guidance to sponsors is of utmost importance to ensure the continued protection of clinical trial subjects and contribute to the high standards of excellence of research and development in Canada;
- Consideration will be given to the impact of emerging technology and adaptive design;
- International harmonization will be sought by adopting or adapting international guidances where appropriate;
- Consistency with Government of Canada policies on regulating including the *Cabinet Directive on Streamlining Regulations* and the commitments in *Advantage Canada* to reduce paperwork burden on business.

In accordance with HPFB's Good Guidance Principles, all guidance reviews will be undertaken horizontally across HPFB Directorates involved in clinical trials of pharmaceuticals and biologics, namely the Therapeutic Products Directorate, the Biologics and Genetic Therapies Directorate, and the Inspectorate to respond to concerns related to consistency and predictability of the interpretation of the regulations across the Branch.

In addition, internal collaboration pertaining to guidance documents will be undertaken, with Health Policy Branch and others within Health Canada and across the Health Portfolio, as necessary. The outcome of the work on a voluntary standard for REBs reviewing clinical trials will be considered.

The following topics will be addressed as Health Canada reviews guidances:

### **Records Retention**

The 2001 regulatory amendments required that sponsors retain documents related to the conduct of the clinical trial, including all versions of the investigator's brochure and adverse events from inside or outside Canada, for a period of 25 years. Concerns related to these requirements were identified during the consultations included accountability for document retention (e.g., where records must be kept, who keeps the records) and the confidentiality of documents and information (e.g., who has access, transfer of patient medical records to the sponsor or between

entities). Stakeholders have also questioned the suitability of the record-keeping requirements in a risk-based approach. For example, whether the record keeping requirements for bioequivalence studies should be the same as those for stem cell research and vaccines. Some have also noted that Canada's records retention period of 25 years is longer than that of other leading regulators.

HPFB officials are reviewing records-retention issues, including a scan of international best practices. Details of what should be kept as part of the records, the storage medium (ie. paper vs electronic) and by whom are also being assessed. It is expected that the analysis will be complete over the Spring 2008 with focussed consultations on revisions to the *Guidance Document for Clinical Trial sponsors as well as to the Guidance for Records related to clinical trials sponsors (GUIDE-0068)*.

Health Canada will also consider the possibility of regulatory amendments for a risk-based approach to records retention requirements. These potential amendments would be consistent with the Progressive Licensing Framework objective of ensuring that the regulatory structure enables Health Canada to implement best international regulatory practices and maintain appropriate oversight without unduly increasing regulatory burden. If regulatory amendments are pursued, focussed consultations will be undertaken with key stakeholders, as well as formal consultations via the Canada Gazette process.

### **Application and notification requirements**

Predictability is an important component of a sponsor's plan for rolling out the various phases of activity involved in clinical trials. Stakeholders indicated a need for clarification around information requirements for Health Canada to review clinical trial applications within 30 days, and further clarification about which applications qualify for the seven-day administrative review target.

Stakeholders also raised concerns regarding the requirements for clinical trial application amendments (CTA-As) which appear burdensome to some groups. Respondents identified the need to clarify the regulatory requirements, streamline processes and review the amount of information that is required. In particular, comments indicated that Health Canada should consider limiting full amendment submissions to filing only substantive changes and to further define "minor" and "major" changes.

Health Canada's review of the *Clinical Trials Manual* and the *Guidance for Clinical Trial Sponsors* will include new information to sponsors regarding information needs and processes related to clinical trial applications, amendments and notifications.

Based on stakeholder input, HPFB is currently revising the protocol safety and efficacy templates referred to as the Pharmaceutical Safety and Efficacy Templates (PSEAT). Health Canada posted the initial draft templates for consultation in January 2007 and the final templates Protocol Safety and Efficacy Assessment Template - Clinical Trial Application (PSEAT-CTA)

were posted in March 2008. HPFB is also revising the clinical trial site information such that it will include an appendix, similar to what is provided in the current HC/SC 3011 form, which will provide additional guidance on how to complete this form.

## **Labelling**

The labelling provisions of *Part C, Division 5* of the *Food and Drug Regulations* specify that the sponsor is responsible to ensure the drug bears a label in both official languages, with the name, number or identifying mark, the expiration date, the recommended storage conditions, the lot number, the sponsor's name and address, the protocol code or identification, and a statement that the drug is investigational to be used only by a Qualified Investigator. Trial drugs may have several labels (shipping box, vials, patient container, etc.), and many trials are conducted with marketed drugs, often taken "off the shelf." Concerns have been raised with regard to the term expiry date, specifically whether the re-test date may be used in lieu of the expiry date, and whether labels should be affixed on package inserts only.

HPFB will develop a guidance document addressing the various labelling requirements for clinical trials including the acceptable format for an expiry date and the use of inner and outer labels. This guidance document will be available in draft for consultation in the fall 2009.

## **Quality Issues**

Certain sponsors commented that Health Canada's quality requirements are comparatively more stringent than those of other jurisdictions. Through consultations with industry organizations and sponsors, most issues have been resolved on a case-by-case basis. Issues that can be generalized in guidance will be addressed in the review of the *Guidance for Sponsors of Clinical Trial Applications - Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications*. A revised document is expected in draft for consultation in the Spring 2008.

## **Good Clinical Practice (GCP) Framework**

Health Canada recognizes that many groups involved in clinical trials, such as academics and not-for-profit organizations which play a critical role in research and development are less familiar with the regulatory requirements for clinical trials listed outlined in *Part C, Division 5* of the *Food and Drug Regulations*, given their limited experience in this area. As such, a compliance promotion strategy will be developed to address the particular information needs of these groups in order to meet their regulatory obligations as they continue to undertake clinical trial activities.

## **Inclusion of Women in Clinical Trials**

Health Canada recognizes the importance of enrolling women in clinical trials at all stages of drug development in order to define the risks and benefits associated with drug therapy in this segment of the population. In general, clinical trials should be composed of representatives of the same segments of society as the sponsor expects to use the drug after market authorization, or the sponsor must present clear scientific reasons for not doing so.

A policy and accompanying guidance document were issued on May 27, 1997 on *Inclusion of Women in Clinical Trials*, following a broad-based consultative process with consumer and health groups, women's organizations, the research community, health professions and the pharmaceutical industry. The review also considered actions by other regulatory agencies on inclusion of women and subpopulations in clinical trials research.

A number of stakeholders have identified a need to review the 1997 Guidance Document, *Inclusion of Women in Clinical Trials*, to ensure it addresses current issues. The document is first being reviewed internally by the Therapeutic Products Directorate's Office of Clinical Trials (TPD-OCT) and the Biologics and Genetic Therapies Directorate (BGTD) to ensure it is consistent with Good Guidance Practices. Further internal review will be undertaken by the Bureau of Women's Health and Gender Analysis, Health Policy Branch, in collaboration with TPD-OCT and BGTD. It is expected that a draft of the revised document on Inclusion of Women in Clinical Trials will be available for consultation in the summer of 2008.

The topics outlined above apply to the following clinical trial guidance documents:

- *Guidance for Clinical Trial Sponsors: Clinical Trial Applications* - Summer 2008 consultation
- *Guidance for Sponsors of Clinical Trial Applications Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTA's)* - Spring 2008
- *Therapeutic Products Programme Guidelines on the Inclusion of Women in Clinical Trials* - Summer 2008 consultation

In addition to the documents outlined above, Health Canada will prepare a new guidance document on the labelling requirements for drugs and biologics used in clinical trials.

Based on the work undertaken on the guidance documents, Health Canada will revise the web-based Clinical Trials Manual which provides an overview of the more detailed guidances related to clinical trials. The manual is designed to provide tools and relevant links to facilitate the successful filing of a CTA to Health Canada. Revisions to the Clinical Trials Manual will also summer 2008.

If necessary, Health Canada will develop new guidances for topics requiring more detailed attention. In order to be effective in meeting the information needs of stakeholders, the drafting and review of guidance documents will be undertaken in consultation with key stakeholders. Consultations on the guidances will begin in the fall of 2008.

## **7 Building on Current Processes for a More Efficient and Effective Regulatory Framework - Summer 2008**

Over the course of the review, a number of measures were identified to improve the efficiency and effectiveness of processes and to strengthen the infrastructure supporting the regulatory framework for clinical trials. In addition to the initiatives outlined below, Health Canada will look to facilitate the submission of clinical trial applications (CTAs) such as electronic receipt and approval of CTAs and a secure e-mail communications system with clinical trials sponsors over the long-term.

### ***Advantage Canada's Reduction of Red Tape for Businesses***

*Advantage Canada*, Canada's long-term economic plan, committed to reducing the paperwork burden on business by 20 percent. Health Canada is considering possibilities of reducing the amount of information required from sponsors without compromising the relevant information required for reviewing a CTA. An example of this includes the revisions currently being made to the Pharmaceutical Safety and Efficacy Assessment Templates (PSEATs).

HPFB is also considering modifying the requirements for clinical trial application amendments (CTA-As) by clarifying that the regulatory obligation to provide a copy of the original protocol can also be met by providing the amended protocol and list of changes, including the rationale for each amendment, electronically and in hard-copy. Only an electronic copy of the old protocol would be required, as opposed to a hard copy.

HPFB also encourages sponsors to submit clinical trial site information forms electronically as the Health Canada continues to explore the possibility of receiving CTAs via the e-Common Technical Document (CTD) format.

### **Adverse Drug Reaction Reporting**

Complete information about a drug includes details of both benefits and risks. Adverse Drug Reactions (ADR) reported on drugs in development are key elements necessary to assess their risk. As required by Division 5 C.05.014 of the *Food and Drug Regulations*, sponsors of drugs undergoing clinical trials in Canada ". . . should report any serious unexpected adverse drug reaction in respect of the drug that has occurred inside or outside Canada". This applies to reports from spontaneous sources and from any clinical or epidemiological investigation. A complete assessment of the safety of a drug includes reports from the clinical trial participants as well as all foreign pre- and post-market reports.

During consultations, stakeholders commented on the need for a more streamlined safety reporting system. As part of its Post Market Surveillance Strategic Plan, Health Canada is proceeding with the launch of the Canada Vigilance System which is a comprehensive suite of products to address safety, pharmacovigilance and risk management needs of Health Canada. The Canada Vigilance system for post-market safety surveillance will be launched in early 2008 and plans are underway within Health Canada to extend the implementation of the system to pre-market activities such as clinical trials.

The Therapeutic Products Directorate, Office of Clinical Trials receives approximately 150 to 200 ADR reports daily and the Biologics and Genetic Therapies Directorate, Clinical Trial Division receives approximately 35 ADR reports daily. These reports are an invaluable source of safety information that must be collected, evaluated and communicated quickly. Implementation of the new Canada Vigilance System for clinical trials will allow cross-referencing between pre and post-market drug safety information throughout the product life-cycle. This will assist in alleviating the duplication in reporting of adverse drug reactions in clinical trials, an issue raised during the consultations.

The periodic review and evaluation of evolving safety information, which is crucial to the ongoing assessment of risk during clinical development of an investigational drug is as important as the expedited review of ADRs. In recognition of the need for an internationally harmonized periodic report for investigational compounds, similar to the Periodic Safety Update Report for marketed products, an ICH Expert Working Group, with representation from Health Canada, was convened to develop an ICH Guideline on Development Safety Update Reports (DSURs). A draft guideline is expected to be published for consultation in the summer of 2008.

### **Building stronger partnerships and support systems for Research Ethics Boards**

The 2001 regulatory framework provided strengthened oversight by requiring all clinical trials for drugs to undergo review and approval by a REB prior to commencement.

REBs play a central role in ensuring the protection of clinical trial subjects within the oversight system of clinical trials in Canada. Not only are REBs mandated to ensure the protection of patient rights, safety and well being, they also perform monitoring and review functions outside of the trial protocol such as compensation, informed consent forms and process, and reviewing local and institutional considerations that may affect the conduct of a trial. Although the role is identified in regulation and guidance, there is often limited information provided on how REBs are expected to fulfil their mandate (e.g., how to act on adverse events reports).

The results of the summer 2006 electronic consultation indicated delays due to the REB process, and that efficiency measures could be introduced to ease the burden including an accreditation system for REBs and the development of national standards as a step in the right direction. In response, Health Canada is supporting two key initiatives to address these issues. These are the Sponsors' Table for Human Research Participant Protection in Canada and the development of a voluntary standard for REBs reviewing clinical trial applications.

In addition to supporting these two initiatives, Health Canada continues to recognize the role of the REBs in the clinical trial process and commits to working with these groups on relevant projects such as the Progressive Licensing Framework.

### **Sponsors' Table for Human Research Participant Protection in Canada:**

Health Canada is partnering with member organizations of the Sponsors' Table for Human Research Participant Protection in Canada ([www.hrppc-pphrc.ca](http://www.hrppc-pphrc.ca)) to promote the highest standards in excellence and ethics in research involving humans.

In large part, research organizations in Canada operate to high ethical standards. The current system of protection for clinical trial subjects faces increasing pressures related to issues such as governance, consistency, transparency and public accountability. To address these pressures, the research community needs a shared vision that can further develop the system to protect research participants while facilitating important research.

Part of the Sponsors' Table for Human Research Participant Protection in Canada process included the establishment of an Experts Committee to provide independent analysis and recommendations. The draft report of the committee entitled "Moving Ahead" was posted for consultation from August to November 2007 on the Sponsors' Table for Human Research Participant Protection in Canada website ([www.hrppc-pphrc.ca](http://www.hrppc-pphrc.ca)). The Experts Committee is now considering the feedback and finalizing its report which will be delivered to the Sponsors' Table for Human Research Participant Protection in Canada for consideration and action as appropriate.

### **Development of a voluntary standard for Research Ethics Boards reviewing clinical trials:**

Health Canada initiated the development of a voluntary standard with the goal of addressing a number of gaps in the current REB system including consistency between REBs, efficiency in REB review, particularly in multi-site trials, quality assurance, and a common approach to ethics review.

The Canadian General Standards Board (CGSB), a federal government organization that offers comprehensive standards development services in support of economic, regulatory, procurement, health, safety and environmental interests, is facilitating the development of a voluntary standard. The standard is being developed by a committee of stakeholders and experts in the field of clinical trials and research ethics.

The CGSB is using a consensus approach in which the committee is responsible for the technical content and approval of the standard. The development of the standard is expected to take up to two years.

The goal of the voluntary standard is to address some gaps and inconsistencies in the current REB system in Canada by bringing stakeholders together in a process to develop operational support and guidance for REBs.

The standard also aims to enhance harmonization by providing REBs that review clinical trials with a common approach to functioning. The standard will also consider the importance of international harmonization and adapting to international developments such as the Council for International Organizations of Medical Sciences (CIOMS) proposal for enhancing the collection, analysis and reporting of safety information from clinical trials known as CIOMS VI.

## **8 Improving Access to Clinical Trial Information - Summer/Fall 2008**

Improving access to information about clinical trials to help patients and health providers make informed health decisions supports the Health Products and Food Branch's goal of providing Canadians with access to safe and effective health products and the information they need to make healthy choices.

HPFB has recently launched a Consumer Information Strategy to help Canadians access authoritative information that meets their needs and allows them to make better decisions about their health by:

- identifying new and effective ways to improve the way HPFB communicates information to consumers;
- improving and expanding the tools, practices, and partnerships through which the Branch communicates information;
- getting information to consumers when they need it and in a way that it can be more easily and more effectively integrated into the choices that they make; and
- adopting some of the best practices from international regulators and other health organizations.

### **Registration and Disclosure of Clinical Trials**

The registration and disclosure of clinical trial information has been identified as a key means of enhancing the transparency of clinical trials, which would support the comprehensive reporting of clinical outcomes and allow Canadians to make more informed decisions about their health.

While Health Canada continues to explore the development of a regulatory requirement for registration and disclosure of results, sponsors are encouraged to register their trials on one of the following publicly accessible registries of the World Health Organization (WHO) Register Network:

- ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov))
- Current Controlled Trials International Standard Randomised Controlled Trials Number Register ([www.controlled-trials.com/isrctn](http://www.controlled-trials.com/isrctn))



Both of these registries collect and display the WHO's Registration Data Set for clinical trials, can be searched free of charge, and accept prospective registration of clinical trials taking place around the world by a variety of sponsors. Health Canada is also examining the creation of a Canadian search portal for clinical trials, which would allow information to be submitted and searched in both French and English.

Numerous domestic and international initiatives are currently underway to encourage or require registration to facilitate access to information about clinical trials. Patients, prescribers, researchers and regulators have all expressed support for increased public disclosure of information pertaining to clinical trials. Registration of clinical trials would be an official means of making information about clinical trials of health products publicly available in a registry. This could help facilitate patient recruitment for trials, mitigate selective reporting of trials, encourage good clinical practices, promote efficient advancement of science, and facilitate systematic reviews and meta-analyses, among other benefits.

Health Canada has conducted extensive consultations with stakeholders on this issue since 2005, including the establishment of an External Working Group to develop and advise on options in 2006. As Health Canada moves forward, it will continue to actively follow the progress being made by the WHO International Clinical Trials Registry Platform working group and is committed to ensuring that a Canadian approach to clinical trial registration be consistent with international efforts, such as those of the WHO.

## **9 Future Trends and Ongoing *Blueprint for Renewal* Initiatives**

The Government of Canada is committed to a performance-based regulatory system that will protect and advance the public interest in the areas of health, safety and security, the quality of the environment, and the social and economic well-being of Canadians. The objectives of this system are:

- Protection of Canadians and their environment;
- Regulation of the economy in the most efficient, timely and cost-effective manner;
- Clear service standards that hold the Government to account for performance;
- Monitoring and reporting on performance to provide pressure for continuing improvement; and
- Ongoing assessment of and adjustment to regulatory approaches to allow for greater cooperation between regulators and orders of government.

Consistent with these commitments, and in addition to the initiatives outlined in this plan, Health Canada will monitor and assess the implications of trends in the domestic and international clinical trials environment and continually adapt its framework to meet its objectives:

- to strengthen protections for clinical trial subjects; and
- to attract and sustain investment in research and development in Canada.

Many factors affect the traditional roles and responsibilities along the drug development cycle, from pre-clinical research through to market access and even to post-market monitoring and surveillance. A key area of consideration is the expanding role of groups not captured in the regulations who are playing an increasingly important role in clinical trials activities, such as data safety monitoring boards (DSMBs).

The influences of science and technology breakthroughs, the changing nature of drug development and the increased participation of various players in the clinical trials environment raise concerns as to the relevance of the roles and responsibilities currently outlined in the regulatory framework. As Health Canada continues to explore these issues, and those of specific populations, it will build on the work underway on the development of a voluntary standard for REBs reviewing clinical trial applications and consult with stakeholders to identify and assess other emerging issues.

### ***Blueprint for Renewal***

The review of the regulatory framework for clinical trials was undertaken in the context of the Health Products and Food Branch (HPFB) *Blueprint for Renewal* which aims to modernize the regulatory system for health products and food. The Progressive Licensing Project and the review of the Special Access Programme are two other important deliverables under the *Blueprint* which will impact the clinical trials environment in Canada. Furthermore, the outcomes of the Clinical Trials Regulatory Review will inform ongoing work on the review of the Regulatory Framework for Investigational Testing of Medical Devices, and clinical trial requirements being considered under the Natural Health Products Regulatory Review.

### **Progressive Licensing Project**

The objective of the Progressive Licensing Project is to create a modern regulatory framework for therapeutic products, including pharmaceuticals and biologics. The current legislative and regulatory framework for pharmaceuticals and biologics is now over 50 years old and is heavily focussed on the pre-market requirements for the marketing of products. Regulators worldwide are moving to a life-cycle approach to regulation that will provide oversight from the early clinical trial stages through to the post-market environment.

A lifecycle approach to regulation will support the assessment of the risks and benefits of products throughout their entire life-cycle, both before and after they reach the market. This approach has been termed Progressive Licensing, as our knowledge about therapeutic products progresses as they continue throughout their lifecycles. Detailed information on this project is available on the [progressive licensing](#) section of the Health Canada website.

The development of the new framework is guided by two goals of a modern regulatory system:

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

As such, three supporting objectives have been identified to support the development of the framework:

- aligning the Progressive Licensing Framework with the system of health care in Canada to achieve positive health outcomes;
- ensuring that the new regulatory structure enables Health Canada to implement the best international regulatory practices and maintain appropriate oversight without unduly increasing regulatory burden; and
- encouraging and making the best use of evolutions in the science of product development and regulation.

As the clinical trial regulations in Division 5 of the *Food and Drug Regulations* are some of the more modern regulatory pieces, they will help achieve the goals described above of a lifecycle approach. The comments and issues raised by stakeholders throughout the Clinical Trials Regulatory Review are being considered in the development of the new framework including electronic receipt of submissions and other information, Development Safety Update Reports, and harmonization with global partners.

### **Review of the Special Access Programmes**

Health Canada's Special Access Programmes (SAP) for drugs and medical devices administer respective emergency provisions in the *Food and Drug Regulations* and the *Medical Devices Regulations* that allow for the authorization of the sale of therapeutic products that cannot otherwise be sold or distributed in Canada to practitioners treating patients with serious or life-threatening conditions when alternatives have failed and/or are not available. The Programmes consider requests from practitioners and health care providers to access products for the emergency treatment of patients under their care.

The two programs provide discretionary access to therapeutic products and are not intended to be mechanisms to promote or encourage the early use of therapeutic products, or to circumvent the regulatory requirements of the pre-market review process. An authorization by the SAP does not constitute an opinion or statement that a drug or medical device is safe, efficacious or of high quality.

In recent years, there has been increasing pressure on Health Canada to ensure that Canadian patients have timely access to new therapeutic products. Although this has primarily fostered changes to the regulatory review process, it has also increased the pressure for the SAP to provide unimpeded access to products during the pre-market phase of development.

In response, Health Canada initiated a comprehensive review of the SAP for drugs and medical devices consisting of three separate sub-projects which include:

- an operational review to evaluate how the SAP for drugs is functioning within its existing framework;
- an ethics review to study the ethical context of the mandate and activities of the SAP; and
- a broad policy/regulatory review, informed by the operational and ethical reviews, to address issues associated with the mandate and scope of SAP. Health Canada undertook consultations at key steps of this project to ensure that all stakeholders and the Canadian public have the opportunity to contribute to this review.

### **Natural Health Products Regulatory Review**

The Natural Health Products Regulatory Review (NHPRR) has identified harmonizing clinical trial requirements under the *Natural Health Product Regulations* with those arising from the clinical trial regulatory review as an issue. Stakeholder feedback, through our e-consultations, has indicated support for this harmonization, if it accounts for the unique nature and risk profile of NHPs. The Natural Health Products Directorate (NHPD) is awaiting the completion of the Progressive Licensing Project and the clinical trials regulatory review before determining the extent to which elements of these initiatives can be adopted or incorporated into the NHP regulatory regime.

### **Regulatory Framework for Investigational Testing of Medical Devices**

Health Canada is considering a number of amendments to the *Medical Device Regulations* which would strengthen its risk management approach for the investigational testing of medical devices. This approach would be consistent with those of other regulatory jurisdictions, as well as with the regulatory framework that Health Canada applies for clinical trials of drugs. This is consistent with the Auditor General's March 2004 Report, which recommended that Health Canada review its approach for managing the risks related to the conduct of investigational testing of medical devices, and take appropriate action to manage these risks.

A Discussion Paper for Consultation was posted from July to October 2007 in order to obtain stakeholder feedback on the proposed changes. Health Canada will consider this input, as well as work that is underway on other Health Canada initiatives relating to clinical trials, in determining next steps. A consultation report will be posted to the Health Canada website in Spring 2008 and information about next steps will also be made available at that time.

## 10 Conclusion

The process undertaken as part of the review of the regulatory framework for clinical trials supports the Government of Canada *Cabinet Directive on Streamlining Regulations* which came into effect on April 1, 2007.

The new directive places a renewed focus on enhanced international cooperation, consideration that the regulatory tool is the most appropriate, and the identification of opportunities for improvement including regulatory amendments and the non-regulatory tools such as policies and guidances to achieve the original regulatory objective.

As Health Canada progresses with implementation of the various initiatives listed in *Clinical Trials Regulatory Review: Targeted Measures for a Strengthened Framework* it will undertake focussed consultations with stakeholders and provinces and territories. Particular outreach efforts will be explored to ensure that the growing range of players involved in the clinical trials environment are given the opportunity to contribute to this strengthened framework.

The following table summarizes the key initiatives to be undertaken over the course of 2008 in response to feedback received during our stakeholder consultations to strengthen and improve the regulatory framework for clinical trials. Stakeholders will also continue to have the opportunity to contribute to ongoing consultations on the Progressive Licensing Framework.

*Clinical Trials Regulatory Review: Targeted Measures for a Strengthened Framework*

<b>Guidance to industry to assist in meeting regulatory obligations - Spring/Summer 2008</b>
Guidance document review to address issues related to: <ul style="list-style-type: none"><li>• Records retention*</li><li>• Application and notification requirements</li><li>• Labelling</li><li>• Quality issues</li><li>• GCP framework</li><li>• Inclusion of women in clinical trials</li></ul> * Health Canada will also consider potential regulatory amendments for a risk-based approach to records retention requirements

<b>Building on current processes for a more efficient and effective regulatory framework - Summer 2008</b>
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| <ul style="list-style-type: none"><li>• Facilitating CTA submissions through electronic receipt and approval mechanisms</li><li>• Streamlining ADR reporting</li><li>• Enhancing the consistency and quality of REB reviews through two initiatives:<ul style="list-style-type: none"><li>• the Sponsors' Table for Human Research Participant Protection in Canada</li><li>• the development of a voluntary standard for REBs</li></ul></li></ul> |
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<b>Improving access to clinical trial information - Summer/Fall 2008</b>
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| <ul style="list-style-type: none"><li>• Implementation of a process for the registration and disclosure of clinical trial information</li></ul> |
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## **Annex 1 - Background of the Clinical Trials Regulatory Framework**

### **Establishment of a new regulatory framework in 2001**

The regulatory requirements respecting drugs used for the purposes of clinical trials were originally developed in the early 1960s under the *Food and Drugs Act*. Over time, the *Act* and related regulations did not keep pace with the changing environment of clinical trials and drug development in Canada, creating gaps in a number of areas. For example, the regulator lacked the authority to investigate and suspend unauthorized trials, to detect instances of sponsors not following an approved trial protocol, or to identify non-reporting of serious and unexpected adverse events.

Regulatory amendments to Part C, Division 5 of the *Food and Drugs Regulations* came into force on September 1, 2001. Their objectives were to strengthen the protection of clinical trial subjects and to attract and sustain investment in research and development.

The new regulatory framework incorporated the following features:

- New authorization requirements for Phase I, II and III clinical trials involving new drugs and drugs whose proposed use would be outside the parameters of the authorized conditions of use (e.g., new indications, dosage regimen, target patient populations).
- Clear and transparent requirements for application amendments, notification, labelling, record keeping and the reporting of serious unexpected adverse drug reactions.
- An inspection program to assess compliance with the *Food and Drugs Act* and its associated regulations and adherence to good clinical practices (GCP) and promote standardization by harmonizing with GCP standards developed by the International Conference on Harmonization (ICH).
- Strengthened oversight of clinical trials requiring that all clinical trials for drugs undergo review and approval by a research ethics board (REB) prior to commencement.

- A 30-day default period for Health Canada to review applications to sell or import a drug for the purpose of a clinical trial (reduced from the previous 60-day default time); and
- Clear Ministerial authority to refuse an application, suspend or cancel the sale of drugs for use in clinical trials in Canada where regulatory requirements are not satisfied.

Health Canada introduced an administrative target of seven days for the review of bioequivalence trials and some Phase I trials in healthy adult volunteers to stimulate clinical research and development in Canada, but was not included in the text of the regulations.

The regulations were structured to place priority on patient safety by further clarifying the roles and responsibilities of stakeholders involved in the clinical trials environment. In particular, the responsibility of sponsors to ensure the safety of trial subjects was more clearly defined, while recognizing the roles of others in the process, including Research Ethics Boards (REBs) and qualified investigators.

### **Implementation of the 2001 regulations**

The 2001 clinical trials regulatory framework brought Canada in line with other regulators by introducing competitive default review periods, establishing an inspection program, awareness and information strategies, increasing harmonization with international standards, and strengthening oversight functions.

### **Implementation of the key components**

#### *Inspection strategy*

The inspection strategy was implemented in 2002 to verify and assess compliance with regulatory requirements, adherence to generally accepted principles of good clinical practices, and the validity of the data generated. The inspection activities began with a voluntary pilot phase with inspections carried out at the request of the sponsor and Qualified Investigators.

Inspection activities cover sponsors, contract research organizations (CROs), research ethics boards (REBs) and Qualified Investigators. These activities involve the verification of source documents such as medical records and drug storage conditions to improve compliance and to further protect the safety of human research subjects. Up to two percent of Canadian clinical trial sites are inspected annually based on a risk management approach to site selection.

In 2003/2004 clinical trials continued to be inspected by the Inspectorate. Results of these inspections were publicly released and are available on the Health Canada website. The Inspectorate is currently working on a summary report of inspections conducted to 2005/2006. This report will also be available to the public.

### *Awareness strategies*

HPFB undertook several outreach activities to raise awareness and educate stakeholders on the new regulatory requirements. These included the development of guidance documents (e.g., chemistry and manufacturing review, record keeping), templates, annual reports and other communications materials, such as the clinical trials application guidelines. Access to information was also facilitated through communications by e-mail as well as the increased availability of on-line information. In addition, Health Canada representatives made numerous presentations and participated in several public forum events and grand rounds with researchers and research coordinators affiliated with regional health centres and research groups. These events enabled the stakeholder community to ask questions and to seek clarification on the new requirements. In 2006, the Branch also launched the clinical trials e-manual to help facilitate the filling of successful applications.

### *Harmonization*

The Branch has actively been engaged in international harmonization forums such as the International Conference on Harmonization (ICH) to develop common standards for the conduct, evaluation and monitoring of clinical trials, as well as for other aspects of drug development and registration such as guidance for data safety reports. In some cases, Health Canada has adopted appropriate ICH documents, with Canadian addenda where necessary to respond to unique Canadian issues and clarify operational requirements.

As well, Health Canada played a leadership role in the development of the ICH Considerations Paper, “Gender Considerations in the Conduct of Clinical Trials” (EMEA 2005). The Paper provides a summary of existing ICH guidelines relevant to gender and of regulatory experiences in the three ICH regions regarding representation of women in pivotal clinical trials and the review determined that there is no need for a separate ICH guideline on gender. ([emea.europa.eu/pdfs/human/ich/391605en.pdf](http://emea.europa.eu/pdfs/human/ich/391605en.pdf))

Health Canada has also been involved in the work of the Council for International Organizations of Medical Sciences on proposals for enhancing the collection, analysis, evaluation, reporting and overall management of safety information from clinical trials known as CIOMS IV.

### *Human research participant protection*

The new framework and inspection system reinforced and validated activities by sponsors, researchers, and other stakeholders which were already underway aimed at promoting research excellence through greater awareness and application of good clinical practice principles, and increasing oversight through monitoring and REB review.



*Review performance, trends in clinical trial applications and research and development*

The introduction of the 30-day default review and the development of templates, guidances and on-line information facilitated processes for the preparation, review and approval of clinical trial applications (CTAs). From September 1, 2001 to March 31, 2002 the number of CTAs for pharmaceuticals increased by 40%, and the number of CTAs for biologics increased by 70%.

From 2002 to 2006, CTAs have increased on average by 6.2% annually for pharmaceuticals and by 9.6% for biologics. Despite this increase of CTAs and the increasing volume of amendments submitted for review, HPFB consistently met the 7-day and 30-day review targets established in 2001.

The following table shows the distribution of CTAs received by category since 2001.

<b>Period (year)</b>	<b>2006</b>	<b>2005</b>	<b>2004</b>	<b>2003</b>	<b>2002</b>	<b>2001*</b>
<b>Phase</b>	<b>Pharmaceuticals</b>					
Joint review	1	6				445
PH1 Bioequivalence - 7 day	908	1006	944	749	630	138
PH1 Healthy Human - 7 day	94	81	85	49	45	9
PH1 Healthy Human - 30 day	4	2	4	4	7	8
PH1 Other - 30 day	55	58	59	53	32	0
PH2 - 30 day	247	226	259	247	211	55
PH3 - 30 day	329	303	324	334	327	96
Phase 1/2 - 30 day	7	10	12	6	6	6
Phase 2/3 - 30 day	8	10	9	4	13	3
Phase unassigned - 30 day	39	38	34	38	16	11
<b>Totals</b>	<b>1686</b>	<b>1740</b>	<b>1730</b>	<b>1484</b>	<b>1287</b>	<b>771</b>
<b>Period (year)</b>	<b>2006</b>	<b>2005</b>	<b>2004</b>	<b>2003</b>	<b>2002</b>	<b>2001*</b>
<b>Phase</b>	<b>Biologics</b>					
PH1 Healthy Human - 30 day	1	7	3	3	4	0
PH1 Other - 30 day	29	11	24	34	25	4
PH2 - 30 day	81	72	69	55	61	16
PH3 - 30 day	138	105	120	87	71	28
Phase 1/2 - 30 day	4	3	5	2	5	0
Phase 2/3 - 30 day	1	0	1	3	6	1
Phase unassigned - 30 day	18	41	36	27	8	5
<b>Totals</b>	<b>272</b>	<b>239</b>	<b>258</b>	<b>211</b>	<b>180</b>	<b>54</b>

\*Regulatory amendments came into force September 1, 2001.