
Regulations Amending the Food and Drug Regulations (1024 – Clinical Trials)

and

Extract from Regulatory Impact Analysis Statement

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AMENDMENTS

1. Paragraph C.01A.002(1)(c)¹ of the Food and Drug Regulations² is replaced by the following:

(c) any activity with respect to a drug that is used only for the purposes of clinical testing in accordance with subsection C.05.006(1) or section C.08.005; and

2. Subsection C.03.202(2) of the Regulations is repealed.

3. Section C.03.208 of the Regulations is amended by adding the word "and" at the end of paragraph (n), by striking out the word "and" at the end of paragraph (o) and by repealing paragraph (p).

4. Part C of the Regulations is amended by adding the following after Division 4:

Division 5

Drugs for Clinical Trials Involving Human Subjects

Interpretation

C.05.001. The definitions in this section apply in this Division.

"adverse drug reaction" means any noxious and unintended response to a drug that is caused by the administration of any dose of the drug. (*réaction indésirable à une drogue*)

"adverse event" means any adverse occurrence in the health of a clinical trial subject who is administered a drug, that may or may not be caused by the administration of the drug, and includes an adverse drug reaction. (*incident thérapeutique*)

"clinical trial" means an investigation in respect of a drug for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the drug, identify any adverse events in respect of the drug, study the absorption, distribution, metabolism and excretion of the drug, or ascertain the safety or efficacy of the drug. (*essai clinique*)

"drug" means a drug for human use that is to be tested in a clinical trial. (*drogue*)

"good clinical practices" means generally accepted clinical practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons, and the good clinical practices referred to in section C.05.010. (*bonnes pratiques cliniques*)

"import" means to import a drug into Canada for the purpose of sale in a clinical trial.
(*importer*)

"investigator's brochure" means, in respect of a drug, a document containing the preclinical and clinical data on the drug that are described in paragraph C.05.005(e).
(*brochure du chercheur*)

"protocol" means a document that describes the objectives, design, methodology, statistical considerations and organization of a clinical trial. (*protocole*)

"qualified investigator" means the person responsible to the sponsor for the conduct of the clinical trial at a clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is

(a) in the case of a clinical trial respecting a drug to be used for dental purposes only, a physician or dentist and a member in good standing of a professional medical or dental association; and

(b) in any other case, a physician and a member in good standing of a professional medical association. (*chercheur qualifié*)

"research ethics board" means a body that is not affiliated with the sponsor, and

(a) the principal mandate of which is to approve the initiation of, and conduct periodic reviews of, biomedical research involving human subjects in order to ensure the protection of their rights, safety and well-being; and

(b) that has at least five members, that has a majority of members who are Canadian citizens or permanent residents under the *Immigration Act*, that is composed of both men and women and that includes at least

(i) two members whose primary experience and expertise are in a scientific discipline, who have broad experience in the methods and areas of research to be approved and one of whom is from a medical discipline or, if the clinical trial is in respect of a drug to be used for dental purposes only, is from a medical or dental discipline,

(ii) one member knowledgeable in ethics,

(iii) one member knowledgeable in Canadian laws relevant to the biomedical research to be approved,

(iv) one member whose primary experience and expertise are in a nonscientific discipline, and

(v) one member who is from the community or is a representative of an organization interested in the areas of research to be approved and who is not affiliated with the sponsor or the site where the clinical trial is to be conducted. (*comité d'éthique de la recherche*)

"serious adverse drug reaction" means an adverse drug reaction that requires in-patient hospitalization or prolongation of existing hospitalization, that causes congenital malformation, that results in persistent or significant disability or incapacity, that is life threatening or that results in death. (*réaction indésirable grave à une drogue*)

"serious unexpected adverse drug reaction" means a serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information set out in the investigator's brochure or on the label of the drug. (*réaction indésirable grave et imprévue à une drogue*)

"sponsor" means an individual, corporate body, institution or organization that conducts a clinical trial. (*promoteur*)

Application

C.05.002.(1) Subject to subsection (2), this Division applies to the sale or importation of drugs to be used for the purposes of clinical trials involving human subjects.

(2) Except for paragraph C.05.003(a), subsections C.05.006(2) and (3), paragraphs C.05.010(a) to (i), section C.05.011, subsections C.05.012(1) and (2), paragraphs C.05.012(3)(a) to (d) and (f) to (h), subsection C.05.012(4) and sections C.05.013, C.05.016 and C.05.017, this Division does not apply to the sale or importation of a drug for the purposes of a clinical trial authorized under subsection C.05.006(2).

Prohibition

C.05.003. Despite sections C.01.014, C.08.002 and C.08.003, no person shall sell or import a drug for the purposes of a clinical trial unless

(a) the person is authorized under this Division;

(b) the person complies with this Division and sections C.01.015, C.01.036, C.01.037 to C.01.040, C.01.040.2, C.01.064 to C.01.067, C.01.070, C.01.131, C.01.133 to C.01.136, and C.01.435; and

(c) if the drug is to be imported, the person has a representative in Canada who is responsible for the sale of the drug.

General

C.05.004. Despite these Regulations, a sponsor may submit an application under this Division to sell or import a drug for the purposes of a clinical trial that contains a substance the sale of which is prohibited by these Regulations, if the sponsor establishes, on the basis of scientific information, that the inclusion of the substance in the drug may result in a therapeutic benefit for a human being.

Application for Authorization

C.05.005. An application by a sponsor for authorization to sell or import a drug for the purposes of a clinical trial under this Division shall be submitted to the Minister, signed and dated by the sponsor's senior medical or scientific officer in Canada and senior executive officer and shall contain the following information and documents:

- (a) a copy of the protocol for the clinical trial;
- (b) a copy of the statement, as it will be set out in each informed consent form, that states the risks and anticipated benefits arising to the health of clinical trial subjects as a result of their participation in the clinical trial;
- (c) a clinical trial attestation, signed and dated by the sponsor's senior medical or scientific officer in Canada and senior executive officer, containing
 - (i) the title of the protocol and the clinical trial number,
 - (ii) the brand name, the chemical name or the code for the drug,
 - (iii) the therapeutic and pharmacological classifications of the drug,
 - (iv) the medicinal ingredients of the drug,
 - (v) the non-medicinal ingredients of the drug,
 - (vi) the dosage form of the drug,
 - (vii) the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the sponsor,
 - (viii) if the drug is to be imported, the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the sponsor's representative in Canada who is responsible for the sale of the drug,

(ix) for each clinical trial site, the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the qualified investigator, if known at the time of submitting the application,

(x) for each clinical trial site, the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the research ethics board that approved the protocol referred to in paragraph (a) and approved an informed consent form containing the statement referred to in paragraph (b), if known at the time of submitting the application, and

(xi) a statement

(A) that the clinical trial will be conducted in accordance with good clinical practices and these Regulations, and

(B) that all information contained in, or referenced by, the application is complete and accurate and is not false or misleading;

(d) the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of any research ethics board that has previously refused to approve the protocol referred to in paragraph (a), its reasons for doing so and the date on which the refusal was given, if known at the time of submitting the application;

(e) an investigator's brochure that contains the following information, namely,

(i) the physical, chemical and pharmaceutical properties of the drug,

(ii) the pharmacological aspects of the drug, including its metabolites in all animal species tested,

(iii) the pharmacokinetics of the drug and the drug metabolism, including the biological transformation of the drug in all animal species tested,

(iv) any toxicological effects in any animal species tested under a single dose study, a repeated dose study or a special study in respect of the drug,

(v) any results of carcinogenicity studies in any animal species tested in respect of the drug,

(vi) any results of clinical pharmacokinetic studies of the drug,

(vii) any information regarding drug safety, pharmacodynamics, efficacy and dose responses of the drug that were obtained from previous clinical trials in humans, and

- (viii) if the drug is a radiopharmaceutical as defined in section C.03.201, information regarding directions for preparing the radiopharmaceutical, the radiation dosimetry in respect of the prepared radiopharmaceutical and a statement of the storage requirements for the prepared radiopharmaceutical;
- (f) if the drug contains a human-sourced excipient, including any used in the placebo,
 - (i) information that indicates the human-sourced excipient has been assigned a drug identification number under subsection C.01.014.2(1) or, in the case of a new drug, issued a notice of compliance under subsection C.08.004(1), as the case may be, or
 - (ii) in any other case, sufficient information to support the identity, purity, potency, stability and safety of the human-sourced excipient;
- (g) if the drug has not been assigned a drug identification number under subsection C.01.014.2(1) or, in the case of a new drug, a notice of compliance has not been issued under subsection C.08.004(1), the chemistry and manufacturing information in respect of the drug, including its site of manufacture; and
- (h) the proposed date for the commencement of the clinical trial at each clinical trial site, if known at the time of submitting the application.

Authorization

C.05.006. (1) Subject to subsection (3), a sponsor may sell or import a drug, other than a drug described in subsection (2), for the purposes of a clinical trial if

- (a) the sponsor has submitted to the Minister an application in accordance with section C.05.005;
- (b) the Minister does not, within 30 days after the date of receipt of the application, send to the sponsor a notice in respect of the drug indicating that the sponsor may not sell or import the drug for any of the following reasons:
 - (i) that the information and documents in respect of the application
 - (A) were not provided in accordance with these Regulations, or
 - (B) are insufficient to enable the Minister to assess the safety and risks of the drug or the clinical trial, or

(ii) that based on an assessment of the application, an assessment of any information submitted under section C.05.009 or a review of any other information, the Minister has reasonable grounds to believe that

(A) the use of the drug for the purposes of the clinical trial endangers the health of a clinical trial subject or other person,

(B) the clinical trial is contrary to the best interests of a clinical trial subject, or

(C) the objectives of the clinical trial will not be achieved;

(c) for each clinical trial site, the sponsor has obtained the approval of the research ethics board in respect of the protocol referred to in paragraph C.05.005(a) and in respect of an informed consent form that contains the statement referred to in paragraph C.05.005(b); and

(d) before the sale or importation of the drug at a clinical trial site, the sponsor submits to the Minister the information referred to in subparagraphs C.05.005(c)(ix) and (x) and paragraphs C.05.005(d) and (h), if it was not submitted in respect of that clinical trial site at the time of submitting the application.

(2) Subject to subsection (3), a sponsor may sell or import a drug for the purposes of a clinical trial in respect of

(a) a new drug that has been issued a notice of compliance under subsection C.08.004(1), if the clinical trial is in respect of a purpose or condition of use for which the notice of compliance was issued; or

(b) a drug, other than a new drug, that has been assigned a drug identification number under subsection C.01.014.2(1), if the clinical trial is in respect of a use or purpose for which the drug identification number was assigned.

(3) A sponsor may not sell or import a drug for the purposes of a clinical trial

(a) during the period of any suspension made under section C.05.016 or C.05.017; or

(b) after a cancellation made under section C.05.016 or C.05.017.

Notification

C.05.007. If the sale or importation of a drug is authorized under this Division, the sponsor may make one or more of the following changes if the sponsor notifies the Minister in writing within 15 days after the date of the change:

- (a) a change to the chemistry and manufacturing information that does not affect the quality or safety of the drug, other than a change for which an amendment is required by section C.05.008; and
- (b) a change to the protocol that does not alter the risk to the health of a clinical trial subject, other than a change for which an amendment is required by section C.05.008.

Amendment

C.05.008. (1) Subject to subsections (4) and (5), when the sale or importation of a drug is authorized under this Division and the sponsor proposes to make an amendment referred to in subsection (2), the sponsor may sell or import the drug for the purposes of the clinical trial in accordance with the amended authorization, if the following conditions are met:

- (a) the sponsor has submitted to the Minister an application for amendment in accordance with subsection (3);
- (b) the Minister does not, within 30 days after the date of receipt of the application for amendment, send to the sponsor a notice in respect of the drug indicating that the sponsor may not sell or import the drug in accordance with the amendment for any of the following reasons, namely,
 - (i) that the information and documents in respect of the application for amendment
 - (A) were not provided in accordance with these Regulations, or
 - (B) are insufficient to enable the Minister to assess the safety and risks of the drug or the clinical trial, or
 - (ii) that based on an assessment of the application for amendment, an assessment of any information submitted under section C.05.009 or a review of any other information, the Minister has reasonable grounds to believe that
 - (A) the use of the drug for the purposes of the clinical trial endangers the health of a clinical trial subject or other person,

- (B) the clinical trial is contrary to the best interests of a clinical trial subject, or
 - (C) the objectives of the clinical trial will not be achieved;
- (c) before the sale or importation of the drug, the sponsor submits to the Minister
- (i) for each clinical trial site, the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of the research ethics board that approved any amended protocol submitted under paragraph (3)(a) or approved any amended statement submitted under paragraph (3)(c), and
 - (ii) the name, address and telephone number and, if applicable, the facsimile number and electronic mail address of any research ethics board that has previously refused to approve any amendment to the protocol, its reasons for doing so and the date on which the refusal was given;
- (d) before the sale or importation of the drug, the sponsor maintains records concerning
- (i) the information referred to in paragraph C.05.005(h), and
 - (ii) the information referred to in subparagraph C.05.005(c)(ix), if any of that information has changed since it was submitted;
- (e) before the sale or importation of the drug in accordance with the amended authorization, the sponsor ceases to sell or import the drug in accordance with the existing authorization; and
- (f) the sponsor conducts the clinical trial in accordance with the amended authorization.
- (2) For the purposes of subsection (1), amendments are
- (a) amendments to the protocol that affect the selection, monitoring or dismissal of a clinical trial subject;
 - (b) amendments to the protocol that affect the evaluation of the clinical efficacy of the drug;
 - (c) amendments to the protocol that alter the risk to the health of a clinical trial subject;
 - (d) amendments to the protocol that affect the safety evaluation of the drug;
 - (e) amendments to the protocol that extend the duration of the clinical trial; and

(f) amendments to the chemistry and manufacturing information that may affect the safety or quality of the drug.

(3) The application for amendment referred to in subsection (1) shall contain a reference to the application submitted under section C.05.005 and shall contain the following documents and information:

(a) if the application is in respect of an amendment referred to in any of paragraphs (2)(a) to (e), a copy of the amended protocol that indicates the amendment, a copy of the protocol submitted under paragraph C.05.005(a), and the rationale for the amendment;

(b) if the application is in respect of an amendment referred to in paragraph (2)(e), a copy of the amended investigator's brochure or an addendum to the investigator's brochure that indicates the new information, including supporting toxicological studies and clinical trial safety data;

(c) if the application is in respect of an amendment referred to in any of paragraphs (2)(a) to (f) and, as a result of that amendment, it is necessary to amend the statement referred to in paragraph C.05.005(b), a copy of the amended statement that indicates the new information; and

(d) if the application is in respect of an amendment referred to in paragraph (2)(f), a copy of the amended chemistry and manufacturing information that indicates the amendment, and the rationale for that amendment.

(4) If the sponsor is required to immediately make one or more of the amendments referred to in subsection (2) because the clinical trial or the use of the drug for the purposes of the clinical trial endangers the health of a clinical trial subject or other person, the sponsor may immediately make the amendment and shall provide the Minister with the information referred to in subsection (3) within 15 days after the date of the amendment.

(5) A sponsor may not sell or import a drug for the purposes of a clinical trial

(a) during the period of any suspension made under section C.05.016 or C.05.017; or

(b) after a cancellation made under section C.05.016 or C.05.017.

Additional Information and Samples

C.05.009. If the information and documents submitted in respect of an application under section C.05.005 or an application for amendment under section C.05.008 are insufficient to enable the Minister to determine whether any of the reasons referred to in paragraph C.05.006(1)(b) or C.05.008(1)(b) exist, the Minister may require the sponsor to submit, within two days after receipt of the request, samples of the drug or additional information relevant to the drug or the

clinical trial that are necessary to make the determination.

Sponsor's Obligations

Good Clinical Practices

C.05.010. Every sponsor shall ensure that a clinical trial is conducted in accordance with good clinical practices and, without limiting the generality of the foregoing, shall ensure that

- (a) the clinical trial is scientifically sound and clearly described in a protocol;
- (b) the clinical trial is conducted, and the drug is used, in accordance with the protocol and this Division;
- (c) systems and procedures that assure the quality of every aspect of the clinical trial are implemented;
- (d) for each clinical trial site, the approval of a research ethics board is obtained before the clinical trial begins at the site;
- (e) at each clinical trial site, there is no more than one qualified investigator;
- (f) at each clinical trial site, medical care and medical decisions, in respect of the clinical trial, are under the supervision of the qualified investigator;
- (g) each individual involved in the conduct of the clinical trial is qualified by education, training and experience to perform his or her respective tasks;
- (h) written informed consent, given in accordance with the applicable laws governing consent, is obtained from every person before that person participates in the clinical trial but only after that person has been informed of
 - (i) the risks and anticipated benefits to his or her health arising from participation in the clinical trial, and
 - (ii) all other aspects of the clinical trial that are necessary for that person to make the decision to participate in the clinical trial;
- (i) the requirements respecting information and records set out in section C.05.012 are met; and
- (j) the drug is manufactured, handled and stored in accordance with the applicable good manufacturing practices referred to in Divisions 2 to 4 except sections C.02.019,

C.02.025 and C.02.026.

Labeling

C.05.011. Despite any other provision of these Regulations respecting labeling, the sponsor shall ensure that the drug bears a label that sets out the following information in both official languages:

- (a) a statement indicating that the drug is an investigational drug to be used only by a qualified investigator;
- (b) the name, number or identifying mark of the drug;
- (c) the expiration date of the drug;
- (d) the recommended storage conditions for the drug;
- (e) the lot number of the drug;
- (f) the name and address of the sponsor;
- (g) the protocol code or identification; and
- (h) if the drug is a radiopharmaceutical as defined in section C.03.201, the information required by subparagraph C.03.202(1)(b)(vi).

Records

C.05.012.(1) The sponsor shall record, handle and store all information in respect of a clinical trial in a way that allows its complete and accurate reporting as well as its interpretation and verification.

(2) The sponsor shall maintain complete and accurate records to establish that the clinical trial is conducted in accordance with good clinical practices and these Regulations.

(3) The sponsor shall maintain complete and accurate records in respect of the use of a drug in a clinical trial, including

- (a) a copy of all versions of the investigator's brochure for the drug;
- (b) records respecting each change made to the investigator's brochure, including the rationale for each change and documentation that supports each change;

- (c) records respecting all adverse events in respect of the drug that have occurred inside or outside Canada, including information that specifies the indication for use and the dosage form of the drug at the time of the adverse event;
 - (d) records respecting the enrollment of clinical trial subjects, including information sufficient to enable all clinical trial subjects to be identified and contacted in the event that the sale of the drug may endanger the health of the clinical trial subjects or other persons;
 - (e) records respecting the shipment, receipt, disposition, return and destruction of the drug;
 - (f) for each clinical trial site, an undertaking from the qualified investigator that is signed and dated by the qualified investigator prior to the commencement of his or her responsibilities in respect of the clinical trial, that states that
 - (i) the qualified investigator will conduct the clinical trial in accordance with good clinical practices, and
 - (ii) the qualified investigator will immediately, on discontinuance of the clinical trial by the sponsor, in its entirety or at a clinical trial site, inform both the clinical trial subjects and the research ethics board of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of clinical trial subjects or other persons;
 - (g) for each clinical trial site, a copy of the protocol, informed consent form and any amendment to the protocol or informed consent form that have been approved by the research ethics board for that clinical trial site; and
 - (h) for each clinical trial site, an attestation, signed and dated by the research ethics board for that clinical trial site, stating that it has reviewed and approved the protocol and informed consent form and that the board carries out its functions in a manner consistent with good clinical practices.
- (4) The sponsor shall maintain all records referred to in this Division for a period of 25 years.

Submission of Information and Samples

C.05.013. (1) The Minister shall require a sponsor to submit, within two days after receipt of the request, information concerning the drug or the clinical trial, or samples of the drug, if the Minister has reasonable grounds to believe that

- (a) the use of the drug for the purposes of the clinical trial endangers the health of a clinical trial subject or other person;
 - (b) the clinical trial is contrary to the best interests of a clinical trial subject;
 - (c) the objectives of the clinical trial will not be achieved;
 - (d) a qualified investigator is not respecting the undertaking referred to in paragraph C.05.012(3)(f); or
 - (e) information submitted in respect of the drug or the clinical trial is false or misleading.
- (2) The Minister may require the sponsor to submit, within seven days after receipt of the request, any information or records kept under section C.05.012, or samples of the drug, in order to assess the safety of the drug or the health of clinical trial subjects or other persons.

Serious Unexpected Adverse Drug Reaction Reporting

C.05.014. (1) During the course of a clinical trial, the sponsor shall inform the Minister of any serious unexpected adverse drug reaction in respect of the drug that has occurred inside or outside Canada as follows:

- (a) if it is neither fatal nor life threatening, within 15 days after becoming aware of the information; and
 - (b) if it is fatal or life threatening, within seven days after becoming aware of the information.
- (2) The sponsor shall, within eight days after having informed the Minister under paragraph (1)(b), submit to the Minister a complete report in respect of that information that includes an assessment of the importance and implication of any findings made.
- (3) Sections C.01.016 and C.01.017 do not apply to drugs used for the purposes of a clinical trial.

Discontinuance of a Clinical Trial

C.05.015. (1) If a clinical trial is discontinued by the sponsor in its entirety or at a clinical trial site, the sponsor shall

- (a) inform the Minister no later than 15 days after the date of the discontinuance;

(b) provide the Minister with the reason for the discontinuance and its impact on the proposed or ongoing clinical trials in respect of the drug conducted in Canada by the sponsor;

(c) as soon as possible, inform all qualified investigators of the discontinuance and of the reasons for the discontinuance, and advise them in writing of any potential risks to the health of clinical trial subjects or other persons; and

(d) in respect of each discontinued clinical trial site, stop the sale or importation of the drug as of the date of the discontinuance and take all reasonable measures to ensure the recovery of all unused quantities of the drug that have been sold.

(2) If the sponsor has discontinued the clinical trial in its entirety or at a clinical trial site, the sponsor may resume selling or importing the drug for the purposes of a clinical trial in its entirety or at a clinical trial site if, in respect of each clinical trial site where the sale or importation is to be resumed, the sponsor submits to the Minister the information referred to in subparagraphs C.05.005(c)(ix) and (x) and paragraphs C.05.005(d) and (h).

Suspension and Cancellation

C.05.016. (1) Subject to subsection (2), the Minister shall suspend the authorization to sell or import a drug for the purposes of a clinical trial, in its entirety or at a clinical trial site, if the Minister has reasonable grounds to believe that

(a) the sponsor has contravened these Regulations or any provisions of the Act relating to the drug;

(b) any information submitted in respect of the drug or clinical trial is false or misleading;

(c) the sponsor has failed to comply with good clinical practices; or

(d) the sponsor has failed to provide

(i) information or samples of the drug as required under section C.05.009 or C.05.013, or

(ii) information or a report under section C.05.014.

(2) Subject to section C.05.017, the Minister shall not suspend an authorization referred to in subsection (1) unless

- (a) the Minister has sent to the sponsor a written notice of the intention to suspend the authorization that indicates whether the authorization is to be suspended in its entirety or at a clinical trial site and the reason for the intended suspension;
 - (b) the sponsor has not, within 30 days after receipt of the notice referred to in paragraph (a), provided the Minister with information or documents that demonstrate that the authorization should not be suspended on the grounds that
 - (i) the situation giving rise to the intended suspension did not exist, or
 - (ii) the situation giving rise to the intended suspension has been corrected; and
 - (c) the Minister has provided the sponsor with the opportunity to be heard in paragraph (b).
- (3) The Minister shall suspend the authorization by sending to the sponsor a written notice of suspension of the authorization that indicates the effective date of the suspension, whether the authorization is suspended in its entirety or at a clinical trial site and the reason for the suspension.
- (4) If the Minister has suspended an authorization, the Minister shall
- (a) reinstate the authorization in its entirety or at a clinical trial site, as the case may be, if within 30 days after the effective date of the suspension the sponsor provides the Minister with information or documents that demonstrate that the situation giving rise to the suspension has been corrected; or
 - (b) cancel the authorization in its entirety or at a clinical trial site, as the case may be, if within 30 days after the effective date of the suspension the sponsor has not provided the Minister with the information or documents referred to in paragraph (a).

C.05.017. (1) The Minister shall suspend an authorization to sell or import a drug for the purposes of a clinical trial, in its entirety or at a clinical trial site, before giving the sponsor an opportunity to be heard if the Minister has reasonable grounds to believe that it is necessary to do so to prevent injury to the health of a clinical trial subject or other person.

(2) The Minister shall suspend the authorization by sending to the sponsor a written notice of suspension of the authorization that indicates the effective date of the suspension, whether the authorization is suspended in its entirety or at a clinical trial site and the reason for the suspension.

(3) If the Minister has suspended an authorization, the Minister shall

- (a) reinstate the authorization in its entirety or at a clinical trial site, as the case may be, if within 60 days after the effective date of the suspension the sponsor provides the Minister

with information or documents that demonstrate that the situation giving rise to the suspension did not exist or that it has been corrected; or

(b) cancel the authorization in its entirety or at a clinical trial site, as the case may be, if within 60 days after the effective date of the suspension the sponsor has not provided the Minister with the information or documents referred to in paragraph (a).

5. Section C.08.003.1² of the Regulations is replaced by the following:

C.08.003.1. The Minister may examine any information or material filed with the Minister by any person pursuant to Division 5 or section C.08.002, C.08.002.1, C.08.003, C.08.005 or C.08.005.1 to establish the safety and effectiveness of the new drug for which the submission or supplement has been filed.

6. (1) The portion of subsection C.08.005(1)⁴ of the Regulations before paragraph (a) is replaced by the following:

C.08.005. (1) Subject to subsection (1.1) and notwithstanding sections C.08.002 and C.08.003, a manufacturer of a new drug may sell it to a qualified investigator to be used solely for the purpose of clinical testing to obtain evidence with respect to the safety, dosage and effectiveness of that new drug, when the following conditions are met:

(2) Section C.08.005 of the Regulations is amended by adding the following after subsection (1):

(1.1) This section applies only in respect of a new drug for veterinary use.

7. (1) The portion of subsection C.08.005.1(1)³ of the Regulations before paragraph (a) is replaced by the following:

C.08.005.1. (1) Every manufacturer who files a new drug submission, an abbreviated new drug submission, a supplement to a new drug submission, a supplement to an abbreviated new drug submission or a submission for the clinical testing of a new drug for veterinary use shall, in addition to any information and material that is required under section C.08.002, C.08.003 and C.08.005, include in the submission or supplement

(2) Subsection C.08.005.1(6)³ of the Regulations is replaced by the following:

(6) Every manufacturer who has filed a new drug submission, an abbreviated new drug submission, a supplement to a new drug submission, a supplement to an abbreviated new drug

submission or a submission for the clinical testing of a new drug for veterinary use, and has any relating clinical case reports or raw data that were not included therein, shall keep those reports or data and shall, within 30 days after receiving a written request from the Minister, submit them to the Minister.

8. Subsection C.08.006(1)3 of the Regulations is replaced by the following:

C.08.006. (1) For the purposes of this section, evidence or new information obtained by the Minister includes any information or material filed by any person pursuant to Division 5 or section C.08.002, C.08.002.1, C.08.003, C.08.005 or C.08.005.1.

9. Paragraph C.08.009(1)(a) of the Regulations is replaced by the following:

(a) to notify the manufacturer of a new drug for veterinary use that the sale of that drug to qualified investigators is prohibited, or

10. Paragraph C.08.017(b)⁵ of the Regulations is replaced by the following:

(b) report immediately to the Director all serious adverse drug reactions associated with the use of the new drug;

TRANSITIONAL

11. An application concerning the sale of a drug for human use for the purposes of a clinical trial that is received under Division 8 of the Food and Drug Regulations before September 1, 2001 is subject to those Regulations and any procedures established under those Regulations as they read at the time the application was received.

COMING INTO FORCE

12. These Regulations come into force on September 1, 2001.

REGULATORY IMPACT ANALYSIS STATEMENT

(This statement is not part of the regulation)

Description

This amendment introduces regulatory requirements for the sale and importation of drugs for use in human clinical trials. The new requirements are located in Division 5 of the *Food and Drug Regulations* and apply to clinical trials in humans using both new and old drugs.

Consequential amendments are required to Division 8 of the *Regulations* to maintain the status quo for clinical trials in animals using new veterinary drugs. Although the Veterinary Drugs Program of the Health Products and Food Branch (the unit in Health Canada responsible for the regulation of veterinary drugs) has indicated that a broader framework is desirable for veterinary drugs, this will be dealt with at a later date.

This framework incorporates the following features:

- a 30-day default review period for applications to sell a drug for the conduct of human drug clinical trials in Canada in Phases I to III of development;
- clear and transparent requirements for application, information, amendments, notification, labeling, record keeping and adverse drug reaction reporting;
- introduction of an inspection system against internationally accepted good clinical practice principles and good manufacturing practices; and,
- clear authority to refuse an application, suspend or cancel the sale of drugs for use in clinical trials in Canada where they do not meet the updated regulatory requirements.

The use of a marketed drug by a physician or dentist for individual patient treatment is not considered to be a clinical trial. The application requirements under this amendment do not apply to clinical trials on marketed drugs where the investigation is conducted within the parameters of the approved Notice of Compliance (NOC) or Drug Identification Number (DIN) application. These trials are often referred to as Phase IV clinical trials. Sponsors must conduct all clinical trials, including Phase IV trials in accordance with the generally accepted principles of good clinical practice.

Current Canadian Situation

In Canada, the responsibility for developing drugs relies on an effective partnership among many stakeholders including industry, the research granting councils, the medical community, the ethics community and the federal government. Within this partnership, the Therapeutic Products

Directorate [TPD] and the Biologics and Genetic Therapies Directorate [BGTD] of Health Canada provide a critical service by ensuring that clinical trials are properly designed and undertaken and that subjects are not exposed to undue risk.

It is also Health Canada's responsibility to ensure that its decisions are made in a timely fashion thereby not discouraging the research and development of human drugs in Canada.

The *Food and Drug Regulations* currently include several provisions which define the requirements for the sale of drugs for use in clinical trials in humans. These investigations are generally divided into four phases depending on the stage of drug development:

Phase I: Initial safety studies on a new drug, including the first administration of the drug into humans, usually conducted in healthy volunteers. These trials may be conducted in patients when administration of the drug to healthy volunteers is not ethical.

Phase I trials are designed mainly to determine the pharmacological actions of the drug and the side effects associated with increasing doses. Pharmacokinetic as well as drug-drug interaction studies are usually considered as Phase I trials regardless of when they are conducted during drug development as these are generally conducted in healthy volunteers. Phase I trials also include trials in which new drugs are used as research tools to explore biological phenomena or disease processes.

Phase II: Clinical trials to evaluate the efficacy of the drug in patients with medical conditions to be treated, diagnosed or prevented and to determine the side effects and risks associated with the drug. If a new indication for a marketed drug is to be investigated, then those clinical trials may generally be considered Phase II trials.

Phase III: Controlled or uncontrolled trials conducted after preliminary evidence suggesting efficacy of the drug has been demonstrated. These are intended to gather the additional information about efficacy and safety that is needed for further risk/benefit assessment of the drug. In this phase, clinical trials are also conducted in special patient populations (e.g., renal failure patients), or under special conditions dictated by the nature of the drug and disease.

Phase IV: All studies performed after the drug has been approved by the regulator for the market, and related to the approved indication. These studies are often important for optimizing the drug's use. They may be of any type but must have valid scientific objectives. Commonly conducted studies include safety studies and studies designed to support use under the approved indication such as mortality and morbidity studies, or epidemiological studies.

The current regulatory requirements respecting drugs to be used for the purposes of clinical trials were originally developed in the early 1960s and have remained essentially unchanged. Those *Regulations* defined specific Investigational New Drug Submission (IND) application requirements which must be complied with before a new drug could be distributed for trial purposes. In 1987, the *Regulations* were amended to introduce a 60 day default period. Since that time TPD, BGTD and the Veterinary Drugs Program, in the case of a veterinary drug, notify the

sponsor within 60 days if its submission is found to be deficient or else the sponsor may proceed. The 60 day default was introduced in 1987 in an attempt to remedy industry's uncertainty in the planning process and to encourage research opportunities in Canada. A move to shorten the review time provided a positive benefit to all Canadians as it permitted faster access to new innovative therapies through the conduct of a clinical trial.

The Directorates currently review the safety, efficacy and quality data submitted by the sponsor and approve the distribution of the drug to the investigator. The Directorates may authorize the sale of the drug if the protocol is scientifically sound and the drug would not pose unacceptable risks to the trial subjects under the proposed conditions of use. The sponsor of the trial is required to maintain accurate records, report adverse drug reactions, and ensure that the investigator adheres to the approved protocol. Trials in humans should be conducted according to generally accepted principles of good clinical practice. These standards provide assurance that the data and reported results are credible and accurate, and that the rights, integrity, and privacy of clinical trial subjects are protected.

The Directorates encourage sponsors to obtain the approval of a Research Ethics Board (REB) prior to conducting trials in Canada. A REB is an independent body, including both men and women, which is responsible for approving the initiation, and conduct of periodic reviews of biomedical research involving human subjects. The principal mandate of the REB is to ensure the protection of the rights, safety and well-being of subjects in the clinical trial. This structure helps to ensure that conflict of interest situations are avoided and that the health and safety of the trial subjects remain the paramount concern. The role of a Canadian REB includes the provision of recommendations concerning a trial's ethical acceptability and conduct. At the present time, there is no accreditation system in Canada for REBs. This situation is being reviewed by Health Canada in conjunction with the Canadian Institutes of Health Research (CIHR), the National Council on Ethics in Human Research (NCEHR) and other stakeholders in the Canadian clinical research community. Some Canadian REBs have limited resources and experience with the review of drug clinical trials.

The Minister of Health can stop the sale of a drug to an investigator if the Minister believes it is in the public interest to do so. This provision in subsection C.08.005(3) of the *Food and Drug Regulations*, has not been used extensively nor has a routine inspection scheme been implemented.

New Regulatory Framework

These *Regulations* have been developed to recognize the generally accepted principles of good clinical practice and internationally competitive submission review time lines. They reflect extensive consultation with stakeholders. A brief summary of the elements contained in the *Regulations* follows.

Good Clinical Practices (GCP)

Sponsors of clinical trials conducted in Canada must be able to demonstrate that the trials are conducted according to generally accepted principles of good clinical practice. These principles include:

- clinical trials must be conducted in accordance with good clinical practices and the applicable regulatory requirement(s).
- before a trial is initiated, foreseeable risks and inconveniences must be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- the rights, safety, and well-being of the trial subjects are the most important considerations and must prevail over interests of science and society.
- the available non-clinical and clinical information on an investigational drug must be adequate to support the proposed clinical trial.
- clinical trials must be scientifically sound, and described in a clear, detailed protocol.
- a trial must be conducted in compliance with a protocol that has received REB approval prior to initiation.
- the medical care given to, and medical decisions made on behalf of, subjects must always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
- each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- freely given informed consent must be obtained from every subject prior to clinical trial participation.
- all clinical trial information must be recorded, handled, and stored in a way that enables its accurate reporting, interpretation and verification.
- the confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- investigational drugs must be fabricated, handled, and stored in accordance with applicable good manufacturing practices (GMP). They must be used in accordance with

the approved protocol.

- systems with procedures that assure the quality of every aspect of the trial must be implemented.

Labeling

Drugs used in clinical trials must be labeled in accordance with specified labeling requirements. These requirements include the following:

- a statement, to ensure that the drug is identified as an investigational drug to be used only by a qualified investigator;
- the name, number, or identifying mark of the drug;
- the expiration date;
- the recommended storage conditions;
- the lot number of the drug;
- the name and address of the sponsor; and
- the protocol code or identification number.

In addition to the above, radiopharmaceuticals must display the radiation symbol required by the *Atomic Energy Control Regulations* and a statement "Caution--Radioactive Material" « Attention-- produit radioactif ».

Adverse Drug Reaction Reporting

The sponsor must report to the TPD or BGTD on an expedited basis any serious unexpected adverse drug reactions based on the reporting schedule contained within the attached *Regulations*. These requirements are consistent with international standards. The *Regulations* also provide the Minister with the authority to request additional information from the sponsor if there is concern respecting the safety of the clinical trial drug and to take action if required.

Records

The sponsor must keep all records related to the conduct of a clinical trial in a format that facilitates verification for the purpose of an inspection. The records must be maintained for a

period of 25 years. The sponsor must submit requested records within 48 hours if safety concerns arise. Additionally, the Minister can request the submission of information within seven days to facilitate an inspection of a site. This will enable Health Canada to investigate health and safety concerns and to respond in a timely fashion.

30-Day Default System

Sponsors wishing to conduct clinical trials in Phases I to III of development must apply under the 30-day default system. The Directorates will establish shorter administrative targets of seven days for the review of bioequivalence trials and Phase I trials in adult healthy volunteers under the 30-day default system. Applications to conduct Phase I clinical trials using somatic cell therapies, xenografts, gene therapies, prophylactic vaccines or reproductive and genetic technologies will not be included in the seven day target system.

Quarterly and annual performance reports will provide a mechanism to publicly report on the Directorates' performance under the seven day target system. These performance statistics will provide the baseline data for an initial evaluation of this initiative, one year following implementation. This will be followed by a comprehensive review of the *Regulations* in three to five years.

Applications must contain the information described in the *Regulations*, including:

- a clinical trial attestation,
- a protocol,
- statements to be contained in each informed consent form, that set out the risks posed to the health of clinical trial subjects as a result of their participation in the clinical trial,
- an investigator's brochure,
- applicable information on human-sourced excipients,
- chemistry and manufacturing information must also be submitted for clinical trials involving drug products which have not received a DIN or NOC.

Applications will be accepted for review without prior REB approval of the informed consent form and protocol. The sponsor must keep copies of undertakings signed by each qualified investigator that the trial will be conducted according to generally accepted principles of good clinical practice. The sponsor must also keep records of attestations signed by the REB that the Board carries out its functions in a manner consistent with these same practices. Prior to the commencement of the clinical trial, the identification of all investigators and REBs is required for each clinical trial site.

The sponsor can proceed with the clinical trial if the Directorates have not objected to the sale or importation of the drug within 30 days after the date of receipt of the clinical trial application and REB approval for the conduct of the trial at the site has been obtained.

The sponsor must submit additional information or samples if the information and documents submitted are insufficient to assess the quality and safety of the drug to be used in the clinical trial. The sponsor must provide the information requested within two calendar days. The application will be rejected if the information is not provided within two days. The current Management of Drug Submissions Policy will be modified to incorporate this concept.

Amendments

Sponsors must submit an application for an amendment prior to introducing the following changes. Applications for an amendment are subject to a 30-day default system. Applications must be filed for:

- changes to the protocol that affect patient selection and monitoring, clinical efficacy and safety requirements, and patient discontinuation;
- changes to the protocol that result in the extension of the duration of the clinical trial; and
- changes to the chemistry and manufacturing information that may affect drug safety and quality. (For example:
 - specifications for the drug where the limits of the test are relaxed or deleted;
 - where a new impurity or degradation product has been identified; and,
 - the addition of new raw materials, solvents, reagents, catalysts or any other material used in the fabrication of the drug substance.)

The sponsor can make the changes described above without prior authorization to limit an unacceptable risk which has been identified. In that case, the sponsor must provide the required information respecting that change within 15 calendar days.

Notification

Sponsors must notify Health Canada of the following changes, within 15 calendar days of the date of the change:

- changes to the chemistry and manufacturing information that do not affect the quality or safety of the drug.
(For example: changes to the specifications for the drug substance where the limits of the test are tightened or additional tests are added)
- changes to the protocol that do not affect the safety of the trial subjects.

Inspection System

Health Canada will inspect clinical trial sites and trial sponsors to ensure that the generally accepted principles of good clinical practice are met. The objectives of the inspection will be to ensure that participants in clinical trials are not subjected to undue risks, to validate the quality of the data generated or to investigate complaints.

The Minister will use the information collected as a result of these inspections to ensure compliance with the regulatory framework and will take enforcement action, when deemed necessary.

Coming Into Force

These *Regulations* will become effective on September 1, 2001. Health Canada is proceeding with staffing actions and implementing new administrative and process measures to provide the required level of increased service.

Submissions received prior to the coming into force of the new framework will be subject to the current 60 day default and the regulatory requirements in place prior to the effective date of these new *Regulations*.

Expectations

This framework has been designed to meet the following objectives:

- shorten the time required for clinical trial application review, without endangering the health and safety of Canadians;
- improve safety mechanisms for clinical trial subjects, such as compliance with generally accepted principles of good clinical practice;
- address the Auditor General's recommendation that the regulator be more involved in the monitoring and follow-up of conduct of clinical trials;
- ensure that Canada has a clinical trial framework which is flexible but contains sufficient safeguards to ensure that the review of clinical trial applications is not unduly delayed as recommended by the Standing Committee on Health in its report "Organs and Tissue Donation and Transplantation: A Canadian Approach" dated April 22, 1999;
- introduce additional operational efficiencies;

- remove obstacles to additional research and development in Canada, where they do not endanger the health and safety of Canadians;
- evaluate the proposed changes and their impact on research and development in Canada and the health and safety of trial subjects;
- ensure that Canadians have improved access to innovative therapies and advice from Canadian physicians with research expertise in these new therapies.

The Directorates will monitor the impact of these changes on the conduct of clinical trials and on the development of drugs in Canada. Health Canada will conduct a policy review to evaluate the impact of these *Regulations* commencing September 1, 2002.

Cost Recovery

Cost recovery initiatives do not apply to the evaluation of clinical trial applications as such is considered a "public good". Funding to implement this regulatory change has been secured through Appropriations. Therefore, Canadian taxpayers provide all the funding to support this review.

International Perspective

In the United States of America (USA), all clinical trial applications are subject to a 30-day default review period. In cases where the U.S. Food and Drug Administration (FDA) has safety concerns regarding an application, a clinical hold may be issued. The sponsor must delay the proposed clinical trial or suspend an ongoing investigation until the issues surrounding the hold are resolved.

In the United Kingdom (UK), Phase I clinical trials in healthy volunteers are currently exempt from regulatory review. European Union member states recently signed a new Directive on clinical trials which mandates a 60 day default review period for the review of clinical trial applications. Implementation of this Directive will harmonize review practices across member jurisdictions. For example, Phase I clinical trials in healthy volunteers in the UK will become subject to an assessment under this new system.

The USA, Japan, the EU and Canada are coordinating their efforts to use a uniform guideline for good clinical practices. This guideline was developed by the International Conference on Harmonization. In addition the European Parliament is in the process of developing a guideline for the performance of inspection function based on the current version of the *Declaration of Helsinki and the Convention du Conseil de l'Europe pour la protection des droits de l'Homme et de la dignité humaine à l'égard des applications de la biologie et de la médecine*. Those guidelines are expected to be adopted by each individual country of the European Community.

The current trends in clinical trial review indicate that:

- there is approximately a 20% annual increase in the number of trials worldwide;
- reports from the United States indicate that over 60 % of all clinical trials are performed overseas with the majority conducted in the United Kingdom;
- Canada ranks 3rd behind the EU and the USA as the location where clinical trials are routinely conducted;
- there are global pressures to harmonize requirements, and expedite trial reviews;
- the use of electronic data has become more widely accepted;
- there are increased ethical concerns about human safety in clinical research;
- there is a need to conduct clinical trials in specific patient populations; and
- clarifications are required to better define the roles and responsibilities of the various players in the review of clinical trials