



Guidance Document

A Guide for the Preparation of Applications for Authorization of Positron-emitting Radiopharmaceuticals for Use in Basic Clinical Research Studies



Published by authority of the
Minister of Health



Date adopted	2014-10-31
Effective date	2014-10-31

Health Products and Food Branch

<p>Our mission is to help the people of Canada maintain and improve their health.</p> <p style="text-align: right;"><i>Health Canada</i></p>	<p>HPFB's Mandate is to take an integrated approach to managing the health-related risks and benefits of health related to health products and food by:</p> <ul style="list-style-type: none">• Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,• Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. <p style="text-align: right;"><i>Health Products and Food Branch</i></p>
--	---

© Minister of Public Works and Government Services Canada 2014

Available in Canada through

Health Canada – Publications
Address Locator 0900C2
Ottawa, Ontario
K1A 0K9

E-mail: publications@hc-sc.gc.ca
Telephone: 613-957-2991, 1-866-225-0709
Fax: 613-941-5366
Teletypewriter: 1-800-465-7735 (Service Canada)

Également disponible en français sous le titre : Guide de préparation de demandes d'autorisation visant des produits radiopharmaceutiques émetteurs de positrons utilisés en recherche clinique fondamentale

Catalogue No. E

ISBN

FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document **may be** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

Table of Contents

1.	Introduction.....	1
1.1	Policy Objective	1
1.2	Policy Statements	1
1.3	Scope and Application	2
1.4	Background	3
1.5	Glossary.....	3
1.5.1	Acronyms	3
1.5.2	Definitions [derived from section C.03.301 of the <i>Regulations</i> and augmented where necessary]	4
2.	Guidance for Implementation	5
2.1	Roles and Responsibilities	5
2.1.1	Sponsor	5
2.1.2	Research Ethics Board [derived from section C.03.306 of the <i>Regulations</i>]	6
2.1.3	Qualified Investigator [derived from section C.03.315 (f) of the <i>Regulations</i>].....	6
2.2	Limits on the Distribution of the Study Drugs	6
2.3	Study Requirements and Criteria	7
2.4	Overview of the Application, Regulatory Review, and Notification Process.....	7
2.4.1	Criteria for Application [derived from section C.03.307(1) of the <i>Regulations</i>]	8
2.4.2	Information Required [derived from section C.03.307(2) of the <i>Regulations</i>]	9
2.5	Good Clinical Practices and Good Manufacturing Practices [derived from section C.03.311 of the <i>Regulations</i>]	10
2.6	Labelling Requirements	10
2.7	Request for Additional Information [derived from section C.03.313 of the <i>Regulations</i>]	10
2.8	Adverse Reaction Reporting [derived from section C.03.314 of the <i>Regulations</i>].....	11
2.9	Records Related to Basic Clinical Research Studies	11
2.10	Discontinuance of a Study [derived from section C.03.316 of the <i>Regulations</i>]	12
2.11	Suspension [section C.03.317 of the <i>Regulations</i>], Reinstatement [section C.03.318 of the <i>Regulations</i>] and Cancellation [section C.03.319 of the <i>Regulations</i>].....	13
3	Contact Information	13

Appendix 1 – Application for Authorization of Positron-emitting Radiopharmaceuticals (PERs) for Use in a Basic Clinical Research Study

Appendix 2 – Study Site Information and Research Ethics Board Attestation

1. Introduction

This Guidance document provides information on the interpretation and application of sections C.03.301 to C.03.320 of the *Food and Drug Regulations* (the *Regulations*) applicable to positron-emitting radiopharmaceuticals (PERs) used in basic clinical research studies. These sections were introduced with the publication of the *Regulations Amending the Food and Drug Regulations (Positron-emitting Radiopharmaceuticals)* in the *Canada Gazette*, Part II on July 4, 2012, thereby making it easier for sponsors to apply for an authorization for their basic clinical research studies involving PERs. These amendments took effect on January 4, 2013.

1.1 Policy Objective

To provide researchers with a streamlined application process for gaining approval to conduct basic clinical research studies using PERs, while keeping sufficient checks and balances in place with respect to the safety and quality for the drugs in use and the health and safety of the study subjects. This document clarifies application and post-authorization requirements and outlines procedures for obtaining authorization.

1.2 Policy Statements

Sponsors of basic clinical research studies must submit an Application for Authorization to Health Canada for authorization to sell or import a study drug for the purpose of a basic clinical research study.

Under the *Food and Drugs Act* and *Regulations*, Health Canada permits the sponsor to sell a drug (in this case, a PER) for a specific use (in this case, a basic clinical research study), provided that certain conditions are met. When Health Canada issues an authorization for the sale of the drug, it is, in essence, giving the sponsor approval to conduct the study.

Sponsors of basic clinical research studies must conduct basic research studies according to generally accepted clinical practices that are designed to protect the rights, safety and well-being of clinical trial subjects and other persons.

Research Ethics Boards (REBs) have an important role in the oversight of the conduct of basic clinical research studies. Sponsors are required by section C.03.307(2)(q) of the *Regulations* to obtain REB approval for each study site prior to filing for authorization at that site.

The *Regulations* were designed to reduce the regulatory paperwork burden placed on researchers performing basic research with PERs, while allowing Health Canada to conduct an appropriate risk assessment of the PER used in the research study in question.

It is the responsibility of the sponsor to ensure that the sale and importation of PERs used in basic clinical research meet the requirements set out within the *Regulations*.

Regulatory decision-making regarding PERs used in human research will be based on the same scientific and regulatory principles on which the *Food and Drug Regulations* are based.

1.3 Scope and Application

The *Regulations* and this Guidance document apply to PERs used in basic clinical research studies that involve human subjects as described in sections C.03.304 and C.03.305 of the *Regulations*. Basic clinical research studies are aimed at advancing scientific knowledge and are not intended to fulfill any immediate diagnostic or therapeutic purposes.

The *Regulations* and this Guidance document apply to PERs used as an investigative tool as part of a clinical trial conducted with another drug.

A basic clinical research study using PERs with a predefined safety profile in humans is exempted from the clinical trial application (CTA) requirements in Part C, Division 5, of the *Regulations* and from the New Drug requirements in Part C, Division 8, of the *Regulations*. Evidence of safety in humans can be provided from studies conducted outside Canada.

The *Regulations* and this Guidance document do not apply to PERs that have not previously been used in humans. For first-use-in-human studies, a CTA must be submitted as per Part C, Division 5, of the *Regulations*.

This Guidance document does not apply to a PER manufactured from a Schedule D bulk process intermediate (i.e. a biologic PER). A CTA is required for all biologic PERs.

In this Guidance document, “shall” and “must” are used to express a requirement, i.e., a provision that the user is obliged to satisfy in order to comply with the regulatory requirements; “should” is used to express a recommendation which is advised but not required; and “may” is used to express an option which is permissible within the limits of the Guidance document.

This Guidance document supersedes the previous Health Canada’s guidance policy *Use of Positron Emitting Radiopharmaceuticals (PERs) in Basic Research* [POL-0053] and guidance document *Factors Considered in the Assessment of Risks Involved in the Use of Certain Positron Emitting Radiopharmaceuticals in Basic Research Involving Humans* (February 24, 2006).

This Guidance document should be read in conjunction with the [Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines: Drugs Used in Clinical Trials \(Guide-0036\)](#) as well as the [Annex to the Good Manufacturing Practices Guidelines Good Manufacturing Practices \(GMP\) for Positron Emitting Radiopharmaceuticals \(PERs\) \(GUI-0071\)](#). The principles and approaches in these guides should be followed for PERs used in basic research.

For further information on clinical trials, including links to various forms, please consult the [Health Canada website](#). The *Regulations* are administered by the Biologics and Genetic Therapies Directorate, Health Products and Food Branch, Health Canada. Any questions concerning the *Regulations* or this Guidance can be sent to the address in section 3 below.

1.4 Background

On January 4, 2013, the regulatory amendments to Part C, Division 3 of the *Food and Drug Regulations* (Positron-emitting Radiopharmaceuticals) came into force.

Prior to the regulatory amendments applicable to PERs, researchers performing basic research in positron emission tomography (PET) with PERs in humans were subject to Part C, Division 5 of the *Food and Drug Regulations* (Drugs for Clinical Trials Involving Human Subjects), and were required to submit clinical trial applications.

It is recognized by Health Canada that the use of PERs in basic research in humans typically poses minimal health risks, provided certain criteria are met. Therefore Health Canada, in collaboration with members of the research community, has developed a more appropriate regulatory oversight for the use of PERs in basic research that reduces and simplifies regulatory requirements while mitigating the risks to humans by ensuring that the PERs used are safe and of high quality. An amendment to Part C, Division 3 of the *Food and Drug Regulations* (Positron-emitting Radiopharmaceuticals) was initiated by Health Canada. On February 24, 2006, the Guidance Document: *Factors considered in the Assessment of Risks involved in the Use of Positron Emitting Radiopharmaceuticals in Basic Research involving Humans* was implemented. This document accompanied a guidance policy *Use of Positron Emitting Radiopharmaceuticals in Basic Research* [POL-0053]. These documents remained in effect until the regulatory amendment regarding the use of positron emitting radiopharmaceuticals in basic research came into force.

As of January 4, 2013, studies that meet the criteria set out in section C.03.305 of the *Regulations* (and outlined in 2.3 of this Guidance document) are subject to the requirements in place for basic clinical research outlined in Part C, Division 3 of the *Regulations*, and the requirements of Part C, Division 5 of the *Regulations* no longer apply.

The *Regulations* introduce a simplified application process for basic clinical research studies using PERs that meet the specified inclusion criteria. The *Regulations* include provisions respecting the submission of an application, good clinical practices, good manufacturing practices, labelling, record-keeping and adverse reaction reporting. Under the simplified application process, the sponsor must submit a completed basic application form and an attestation form to Health Canada for review. Sponsors are required to maintain records for 5 years instead of 25 years as required under the clinical trial regulations.

The responsibility of research ethics boards with respect to basic clinical research studies using PERs will remain the same as their responsibilities to oversee clinical trials under the clinical trial regulations. However, the sponsor is required to obtain REB approval of the basic clinical research study prior to the sponsor's submission of an application to Health Canada.

1.5 Glossary

1.5.1 Acronyms

ADR Adverse Drug Reaction

BGTD	Biologics and Genetic Therapies Directorate
BRAP	Basic Research Applications: PERs
CIOMS	Council for International Organizations of Medical Sciences
CTA	clinical trial application
GCP	good clinical practices
MBq	Megabecquerel
mCi	millicurie
mSv	millisievert
PER	positron-emitting radiopharmaceutical
REB	research ethics board
rem	Roentgen equivalent in man

1.5.2 Definitions [derived from section C.03.301 of the *Regulations* and augmented where necessary]

Adverse reaction

An undesirable and unintended response in a study subject or other person to a study drug that is caused by the administration of any dose of the study drug. (Réaction indésirable)

Good clinical practices

Generally accepted clinical practices that are designed to protect the rights, safety and well-being of study subjects and other persons. (Bonne pratiques cliniques)

Import

In respect of a study drug, to import it into Canada for sale for the purpose of a study. (Importer)

Other person

An individual who comes into physical contact with a study subject. (Autre personne)

Protocol

A document that describes the objectives, design, methodology, statistical considerations and organization of a study. (Protocole)

Qualified investigator

The physician and member in good standing of a professional medical association in Canada to whom a sponsor gives the responsibility for the proper conduct of the study at a given study site, who is entitled to practise their profession under the laws of the province where the study site is located. (Chercheur qualifié)

Research Ethics Board

A decision-making body that is not affiliated with the sponsor, whose principal mandate is to approve the initiation of and to periodically review biomedical research that involves human subjects in order to protect their rights, safety and well-being. (Comité d'éthique de la recherche)

Sell

To offer for sale, to expose for sale, to have in possession for sale or to distribute, whether or not the distribution is made for consideration (Section 2 of the Food and Drugs Act). (Vente)

Serious adverse reaction

An adverse reaction that results in any of the following consequences for the study subject or other person:

- their in-patient hospitalization or its prolongation;

- a congenital malformation;
- persistent or significant disability or incapacity;
- a life-threatening condition; or
- death. (Réaction indésirable grave)

Serious unexpected adverse reaction

A serious adverse reaction that is not identified in nature, severity or frequency in the risk information set out in the labelling of the study drug. (Réaction indésirable grave et imprévue)

Sponsor

An individual, institution or organization that is responsible for the conduct of a study. (Promoteur)

Study

A basic clinical research study in respect of a positron-emitting radiopharmaceutical that has been previously shown to be safe in human subjects that meets the following inclusion and exclusion criteria:

The purpose of the study is to obtain data on any of the following:

- the pharmacokinetics or metabolism of the study drug;
- normal human biochemistry or physiology; or
- changes caused to human biochemistry or physiology by aging, disease or medical interventions.

The study is not primarily intended to do any of the following:

- discover, identify or verify the pharmacodynamic effects of the study drug;
- identify adverse reactions;
- fulfill an immediate therapeutic or diagnostic purpose; or
- ascertain the safety or efficacy of the study drug. (Étude)

Study drug

Means a specific PER product that is used in a study. A study drug must have been previously tested in humans and must not be manufactured from a bulk process intermediate that is of biological origin. (Drogue destinée à l'étude)

Study site

The location where all or part of a study is conducted. (Lieu d'étude)

2. Guidance for Implementation

2.1 Roles and Responsibilities

2.1.1 Sponsor

The sponsor is an individual, institution or organization that is responsible for conducting the basic clinical research study. The sponsor's responsibilities include, but not limited to: submitting an application for authorization for the study drug; ensuring that the study is conducted according to good clinical practices; fulfilling the requirements with respect to labelling and records management; providing additional information as requested by the Minister; reporting serious and unexpected adverse reactions; sending written notification to the qualified investigator when a study is discontinued and providing reasons for discontinuance;

and also notifying the Minister and REB regarding the discontinuance of the study if the reason for the discontinuance is related to the health or safety of the study subjects or other persons.

The sponsor is responsible for the sale and use of the study drug and ensuring compliance with all applicable laws.

2.1.2 Research Ethics Board [derived from section C.03.306 of the *Regulations*]

The research ethics board approves the initiation of and periodically reviews biomedical research that involves human subjects in order to protect the rights, safety, and well-being of the subjects.

The board shall have at least five members, a majority of whom are Canadian citizens or permanent residents under the *Immigration and Refugee Protection Act*, is composed of both men and women and includes at least:

- i) two members whose primary experience and expertise are in a scientific discipline, who have a broad experience in methods and areas of research to be approved and one of whom is from a medical discipline,
- ii) one member knowledgeable in ethics
- iii) one member knowledgeable in Canadian laws relevant to the research to be approved,
- iv) one member whose primary experience and expertise are in a non-scientific 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 with the study site.

The REB cannot have any affiliations with the sponsor that could compromise its ability to fulfil its principal mandate, or might be perceived to so.

An REB attestation that the study, protocol and informed consent forms have been reviewed and approved must be provided for each study site.

The sponsor is required to seek REB approval prior to filing an application with Health Canada.

2.1.3 Qualified Investigator [derived from section C.03.315 (f) of the *Regulations*]

The qualified investigator is a physician and member in good standing of a professional medical association in Canada to whom a sponsor gives the responsibility for the proper conduct of the study at a given study site in accordance with the *Food and Drug Regulations* and good clinical practices (GCP). Additionally, the qualified investigator is responsible for immediately informing the study subjects if the study is discontinued prematurely, including the reason(s) for the discontinuance and information about any potential risk to the health of the study subjects or other persons.

2.2 Limits on the Distribution of the Study Drugs

No drug can be sold in Canada unless Health Canada has issued an authorization for that sale through one of the regulatory mechanisms outlined in the *Regulations*.

The prohibitions to sale in section C.05.003 (for clinical trial drugs) and sections C.08.002 and C.08.003 (for new drugs) do not apply to PERs used in basic clinical research.

In accordance with Part C, Division 3, section C.03.303, a study drug for human use may not be sold or imported unless:

- a) it is for use in a study;
- b) it has been previously tested in humans and its safety in humans has been demonstrated;
- c) if the study drug is to be imported, the manufacturer of the drug has a representative in Canada who is responsible for its sale;
- d) the sponsor has applied for and been issued an authorization to sell the study drug; and
- e) the sponsor complies with the provisions of the *Regulations* with respect to the study drug.

2.3 Study Requirements and Criteria

To qualify as a basic research study, all the following requirements must be met, as outlined in section C.03.305 of the *Regulations*. The sponsor will be asked to verify these criteria in checklist format on the application form.

- a) There is sufficient data on the testing of the study drug in animals and humans to demonstrate the drug's safety in humans. This information can be obtained through original research or from the body of scientific literature. An appropriately evaluated, Phase I safety study conducted in a country that adopts International Conference of Harmonisation (ICH) guidelines is considered as sufficient data. Alternatively, subject to regulatory discretion, a thorough analysis of historical data available from human exposure obtained outside a Phase I safety study is considered sufficient.
- b) The amount of active ingredients or combination of active ingredients in the study drug has been shown not to cause any clinically detectable pharmacodynamic effects in humans.
- c) The total radiation dose incurred annually by a study subject, including from multiple doses of the study drug, from significant contaminants or from impurities and from the use of other procedures for the purposes of the study, shall not be more than 50 mSv.
- d) Any concomitant drug used in the study has been assigned a drug identification number and is authorized for sale in Canada.
- e) Study subjects shall be at least 18 years old and have legal capacity at the time of the study.
- f) Female subjects shall:
 - i) confirm they are not pregnant, either by way of a pregnancy test or by provision of written confirmation; and
 - ii) be advised that, if they are lactating, they are to suspend breast feeding for at least 24 hours after the administration of the study drug.
- g) The study shall not involve more than 30 subjects unless the sponsor provides an acceptable scientific rationale to Health Canada.

2.4 Overview of the Application, Regulatory Review, and Notification Process

Prior to commencing a basic clinical research study, the researcher (referred to as the sponsor) is required to submit an Application for Authorization of Positron-emitting Radiopharmaceuticals (PERs) for Use in a Basic Clinical Research Study (Appendix 1) as well as a Study Site Information and Research Ethics Board Attestation (Appendix 2) or a Research Ethics Board approval letter that includes the Research Ethics Board certification statement to the Biologics and Genetic Therapies Directorate (BGTD). These submissions are referred to as Basic Research Applications: PERs (BRAP). Applications should be sent to the address in section 3 below.

Within 15 business days of receiving the completed Application for Authorization form, and if the application is complete and all the requirements have been met, BGTD will issue an authorization to sell the PER for the purposes of the study as described in the application.

If the application is complete but the requirements have not been met, BGTD will issue a Not-Satisfactory-Notice to indicate the sponsor has not received authorization for the sale of the study drug. If the sponsor still wants to pursue the clinical trial, a Clinical Trial Application may be filed for a formal review and authorization prior to initiating the study.

If clarification on information provided in the application is required, BGTD will issue a *Clarifax* to request additional information. The sponsor is required to provide the requested information within 2 business days of receipt of the *Clarifax*. BGTD will then review the additional information and inform the sponsor whether the requirements have been met.

The sponsor must send a written notification to Health Canada of the day on which the sale or importation of the study drug is intended to start. This notification must take place at least 15 business days ahead of the date of the first sale.

Any change to the application must be communicated to Health Canada by submitting a revised Appendix 2 for information. These changes may include, but are not limited to, a change of an ongoing site, the addition of a new site, the change/addition of a study start date, a change in the qualified investigator, and/or a change to the REB. If one of the attested criteria in Appendix 1 changes to a “no”, then the sponsor is advised to file a Clinical Trial Application for a formal review in order to obtain authorization to conduct the study.

It is the sponsor’s responsibility to maintain records of any amendments to the study protocols and informed consent forms. Sponsors are not required to submit these amendments to Health Canada.

2.4.1 Criteria for Application [derived from section C.03.307(1) of the *Regulations*]

An application for authorization by a sponsor to sell or import a study drug must contain sufficient information to meet all of the following criteria:

- a) the use of the study drug will not endanger the health of any study subject or other person (with evidence including data from human studies);
- b) the study is not contrary to the best interests of the study subjects; and
- c) the objectives of the study can reasonably be achieved.

The study drug must have previously been tested in human subjects and its safety in humans demonstrated successfully. If the PER and the source of its manufacturing have been previously reviewed and authorized by BGTD in a CTA, the control number of any previous CTA should be identified in Appendix 1, Part 1 (C).

2.4.2 Information Required [derived from section C.03.307(2) of the *Regulations*]

An application for authorization to sell or import a study drug for use in a study shall include all of the following information:

- a) the title of the study and the protocol code or identification;
- b) the purposes and a concise description of the study;
- c) the number of study subjects;
- d) the brand name, if any, of the study drug;
- e) the chemical or generic name of the active ingredients in the study drug;
- f) a qualitative list of the non-active ingredients of the study drug;
- g) the maximum mass of the study drug to be administered to each study subject;
- h) the radioactive dose range of the study drug, expressed in MBq or mCi;
- i) the effective dose or effective dose equivalent of the study drug as determined from human dosimetry studies or a combination of data from human safety studies and animal dosimetry studies with appropriate rational expressed in mSv/MBq or rem/mCi;
- j) the sponsor's name and civic address, their postal address if different, and its telephone number, fax number and email address;
- k) the manufacturer's name and civic address, their postal address if different, and their telephone number, fax number and email address;
- l) in the case of an application for importation, the name and civic address, the postal address if different, and the telephone number, fax number and email address of the manufacturer's representative in Canada who is responsible for the sale of the study drug;
- m) the name and civic address for each study site;
- n) for each study site, the name, civic address telephone number, fax number and email address of the qualified investigator;
- o) the proposed starting date for the study for each study site, if known;
- p) for each study site, the name, civic address, telephone number, fax number and email address of the research ethics board;
- q) a statement, dated and signed by the research ethics board for each study site, that certifies that it has reviewed and approved the study, the protocol and the statement of the risks and anticipated benefits arising to the health of study subjects as a result of participating in the study that is set out in the informed consent form;
- r) a list of any previous applications for an authorization to sell or import a drug for a study related to the current study; and
- s) a statement, dated and signed by the sponsor's senior medical or scientific officer in Canada and senior executive officer, that certifies the following:
 - i) the study will meet the requirements in the *Food and Drug Regulations*; and
 - ii) all of the information contained or referred to in the application is complete and accurate and is not false or misleading.

Health Canada developed Appendix 1 and Appendix 2 for sponsors to use in filing an application, and facilitating the review of the information required. Sponsors should complete these Appendices and file them along with a covering letter that is dated and signed by a sponsor representative. Applications should be sent to the address in section 3 below.

2.5 Good Clinical Practices and Good Manufacturing Practices [derived from section C.03.311 of the *Regulations*]

As stated within subsection C.03.311, good clinical practices, which include good manufacturing practices (GMP), must be followed. The manufacture of study drugs must meet the requirements in Part C, Division 2 of the *Regulations*, other than section C.02.019, C.02.025 and C.02.026.

The principles and approaches in *Guide-0036 – Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines: Drugs Used in Clinical Trials* as well as the *Annex to the Good Manufacturing Practices Guidelines Good Manufacturing Practices (GMP) for Positron Emitting Radiopharmaceuticals (PERs) (GUI-0071)* should be followed for study drugs used in basic research.

2.6 Labelling Requirements

As required in Part C, Division 3, section C.03.312 of the *Regulations*:

Despite any other provisions of these Regulations respecting labelling, the sponsor shall ensure that the study drug:

- a) bears an inner label that sets out both of the following:
 - i. The unique batch number for the study drug, and
 - ii. The radiation warning symbol set out in Schedule 3 to the *Radiation Protection Regulations* and the words “RAYONNEMENT – DANGER – RADIATION”; and
- b) is accompanied by a package insert that sets out all of the following information:
 - i. a statement that indicates that the study drug is to be used only under the supervision of a qualified investigator;
 - ii. the chemical or generic name of the active ingredients in the study drug;
 - iii. the name and civic address of the manufacturer;
 - iv. the name and civic address of the sponsor;
 - v. the code or other identification of the protocol or protocols if the study drug is used in more than one protocol;
 - vi. the warnings and precautions in respect of the use of the study drug; and
 - vii. the possible adverse reactions, if any, associated with the use of the study drug.

2.7 Request for Additional Information [derived from section C.03.313 of the *Regulations*]

Health Canada may, at any time, send a written request to the sponsor for additional information to establish the safety of the study drug if there is reason to believe any of the following:

- a) the use of the study drug may endanger the health of the study subject or other person;
- b) the study may be contrary to the best interests of the study subjects;
- c) a qualified investigator is not respecting the requirements within subsection C.03.315(3)(f); or
- d) information about the study drug or study that was submitted previously is false or misleading.

Additionally, Health Canada may request that the sponsor provide any information or records referred to in Part C, Division 3, subsection C.03.315 (3) of the *Regulations*, in order to assess the safety of the study drug or the health of the study subjects or other persons.

The sponsor must submit the information by the date specified by Health Canada.

2.8 Adverse Reaction Reporting [derived from section C.03.314 of the *Regulations*]

If a serious adverse reaction or serious unexpected adverse reaction has occurred during the course of a study, inside or outside Canada, the sponsor must notify the Minister if:

- a) it is fatal or life-threatening, within 7 calendar days after becoming aware of the information; or
- b) it is not fatal or life-threatening, within 15 calendar days after becoming aware of the information.

Each adverse drug reaction (ADR) which is subject to expedited reporting to Health Canada should be reported individually in accordance with the data element(s) specified in the [Health Canada Guidance for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting ICH Topic E2A](#).

When submitting an ADR report to Health Canada, a complete ADR Expedited Reporting Summary Form (Form 01-03) and the CIOMS Form should be attached and mailed or faxed to the address in section 3 below.

Once the sponsor has notified the Minister as described above, the sponsor must submit to the Minister a complete report in respect of the information, within 8 days, including an assessment of the importance and implications of the findings made.

There are situations in addition to the above that may necessitate rapid communication to Health Canada, and appropriate scientific and medical judgement should be applied to each situation. Refer to the [Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications](#) for examples of these types of situations. Any questions concerning the *Regulations* or this Guidance can be sent to the address in section 3 below.

2.9 Records Related to Basic Clinical Research Studies

As required in Part C, Division 3, section C.03.315 of the *Regulations*:

- 1) The sponsor shall record, handle and store all information in respect of a study in a way that allows it to be reported completely and accurately and to be interpreted and verified.
- 2) The sponsor shall maintain complete and accurate records to establish that the study is conducted in accordance with the *Regulations*.
- 3) The sponsor shall maintain all of the following records in respect of the use of the study drug in each study, including:
 - a) records respecting all adverse reactions that occur inside or outside Canada, including the indications for use and the dosage form of the study drug at the time of the adverse reaction;
 - b) written procedures for subject monitoring and for the documentation and reporting of adverse reactions;
 - c) articles from scientific journals or other publications that were used in support of the safety profile of the study drug in respect of humans;
 - d) records in respect of each study subject, including respecting their enrolment, a copy of their signed consent form and sufficient information to enable them to be identified and contacted in the event that the sale of the study drug may endanger their health or that of another person;
 - e) records respecting the shipment, receipt, sale, return and destruction or other disposition of the study drug;
 - f) for each study site, an undertaking, dated and signed by the qualified investigator before the start of the study, that they will
 - i. conduct the study in accordance with good clinical practices, and
 - ii. on discontinuance of the study by the sponsor, for any reason related to health or safety, immediately inform both the study 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 study subjects or other persons;
 - iii. for each study site, a copy of the informed consent form; and
 - iv. for each study site, a copy of the certifying statement described in paragraph C.03.307(2)(q), of the protocol for the study and of the statement of the risks and anticipated benefits arising to the health of study subjects as a result of participating in the study that is set out in the informed consent form.
- 4) The sponsor shall maintain all records for five years after the day on which the study ends.

The information management system shall allow for the complete and accurate recording of the results of the study so that these results may be interpreted and verified at a later date. The sponsor's records should provide evidence that the study was conducted according to GCP.

2.10 Discontinuance of a Study [derived from section C.03.316 of the *Regulations*]

If a sponsor discontinues a study in its entirety or at a study site, the sponsor must notify all qualified investigators of the discontinuance as soon as possible in writing. The sponsor must

disclose reasons for the discontinuance and whether the study presented any risks to the health of study subjects or other persons.

If the discontinuance is for reasons that would affect the health or safety of study subjects or other persons, the sponsor must notify Health Canada in writing within 15 days after the discontinuance. The notice must include the reasons for the discontinuance and state whether it will have an impact on any proposed or ongoing studies in respect of the study drug in Canada by the sponsor.

2.11 Suspension [section C.03.317 of the *Regulations*], Reinstatement [section C.03.318 of the *Regulations*] and Cancellation [section C.03.319 of the *Regulations*]

There are provisions in the *Regulations* for the suspension or cancellation of the authorization for the sale of the study drug if it is believed that the health and safety of study subjects is at risk; if the sponsor has provided false, misleading or incomplete information; or if the sponsor has failed to meet the requirements for the reporting of adverse reactions.

A suspended authorization may be reinstated if the sponsor can demonstrate the reasons for the suspension are not valid.

Further details of these provisions can be found in the *Regulations* in the above noted sections.

3 Contact Information

3.1 Office of Regulatory Affairs

Inquiries and information requests regarding this Guidance document and serious adverse reaction reports should be submitted directly to:

[Office of Regulatory Affairs](#)

Biologics and Genetic Therapies Directorate
Health Products and Food Branch
Health Canada
200 Tunney's Pasture Driveway,
Address Locator 0701A
Tunney's Pasture,
Ottawa, Ontario
K1A 0K9

E-mail: bgtd_ora@hc-sc.gc.ca

Telephone: 613-957-1722

Facsimile: 613-946-9520

Teletypewriter: 1-800-465-7735 (Service Canada)

3.2 Basic Research Application: PERs (BRAP) submissions

All Basic Research Application: PERs (BRAP) submissions should be sent (via e-mail) to BGTDPTG.BRA.DAERF@hc-sc.gc.ca.