CANADA
PRIVY COUNCIL • CONSEIL PRIVÉ

P.C. 2012-812
June 19, 2012

His Excellency the Governor General in Council, on the recommendation of the Minister of Health, pursuant to subsection 30(1) of the *Food and Drugs Act*, hereby makes the annexed *Regulations Amending the Food and Drug Regulations (Positron-emitting Radiopharmaceuticals)*.

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CLERK OF THE PRIVY COUNCIL–LE GREFFIER DU CONSEIL PRIVÉ

REGULATIONS AMENDING THE FOOD AND DRUG REGULATIONS (POSITRON-EMITTING RADIOPHARMACEUTICALS)

AMENDMENTS

1. Subsection C.01A.002(1) of the *Food and Drug Regulations*[1] is amended by adding the following after paragraph (*b*):

(*b.1*) any activity with respect to a positron-emitting radiopharmaceutical that is used only for the purposes of a basic clinical research study described in section C.03.304;

2. Subparagraph C.03.202(1)(*b*)(vi) of the Regulations is replaced by the following:

(vi) the radiation warning symbol set out in Schedule 3 to the *Radiation Protection Regulations* and the words "RAYONNEMENT — DANGER — RADIATION",

3. Paragraph C.03.203(1)(*f*) of the Regulations is replaced by the following:

(*f*) the radiation warning symbol set out in Schedule 3 to the *Radiation Protection Regulations* and the words "RAYONNEMENT — DANGER — RADIATION";

4. Section C.03.204 of the Regulations is replaced by the following:

C.03.204. (1) No person shall sell a drug that contains technetium-99m at any time during its useful life if it also contains a radionuclidic impurity set out in the monograph for Sodium Pertechnetate Tc-99m Injection referred to in the publication set out in item 8 of Schedule B to the Act, in an amount greater than that shown in the monograph.

(2) No person shall sell a radionuclide generator from which can be removed a drug that contains technetium-99m, at any time during the useful life of the drug, if the drug also contains a radionuclidic impurity set out in the monograph for Sodium Pertechnetate Tc-99m Injection referred to in the publication set out in item 8 of Schedule B to the Act, in an amount greater than that shown in the monograph.

5. The Regulations are amended by adding the following after section C.03.209:

Positron-emitting Radiopharmaceuticals

Interpretation

C.03.301. The following definitions apply in this section and in sections C.03.302 to C.03.319.

"adverse reaction" means 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*)

[1] C.R.C., c. 870

"good clinical practices" means generally accepted clinical practices that are designed to protect the rights, safety and well-being of study subjects and other persons. (*bonnes pratiques cliniques*)

"import" means, in respect of a study drug, to import it into Canada for sale for the purpose of a study. (*importer*)

"other person" means an individual who comes into physical contact with a study subject. (*autre personne*)

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

"qualified investigator" means 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" means a body described in section C.03.306. (*comité d'éthique de la recherche*)

"serious adverse reaction" means an adverse reaction that results in any of the following consequences for the study subject or other person:

(*a*) their in-patient hospitalization or its prolongation;

(*b*) a congenital malformation;

(*c*) persistent or significant disability or incapacity;

(*d*) a life-threatening condition; or

(*e*) death. (*réaction indésirable grave*)

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

"sponsor" means a person who is responsible for the conduct of a study. (*promoteur*)

"study" means a basic clinical research study that involves human subjects and that is described in sections C.03.304 and C.03.305. (*étude*)

"study drug" means a positron-emitting radiopharmaceutical that is used in a study. (*drogue destinée à l'étude*)

"study site" means the location where all or part of a study is conducted. (*lieu d'étude*)

Application

C.03.302. (1) Sections C.03.303 to C.03.319 apply to the sale and importation of study drugs.

(2) Sections C.03.001 to C.03.209 and Divisions 5 and 8 do not apply to study drugs.

(3) Sections C.03.303 to C.03.319 do not apply to a study drug manufactured from a bulk process intermediate that is of biological origin.

Prohibition

C.03.303. No person shall sell or import a study drug unless all of the following requirements are met:

(*a*) the study drug is for use only in a study;

(*b*) the study drug has been previously tested in human subjects 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 is authorized under section C.03.309 to sell or import the study drug; and

(*e*) the sponsor complies with sections C.03.310 to C.03.316.

Purpose of Study

C.03.304. (1) The purpose of a study is to obtain data on any of the following:

(*a*) the pharmacokinetics or metabolism of the study drug;

(*b*) normal human biochemistry or physiology; or

(*c*) changes caused to human biochemistry or physiology by aging, disease or medical interventions.

(2) A study is not primarily intended to do any of the following:

(*a*) discover, identify or verify the pharmacodynamic effects of the study drug;

(*b*) identify adverse reactions;

(*c*) fulfil an immediate therapeutic or diagnostic purpose; or

(*d*) ascertain the safety or efficacy of the study drug.

Requirements

C.03.305. (1) A study shall meet all of the following requirements:

(*a*) before the study drug is used in the study, there is sufficient data from testing it in animals and humans to demonstrate its safety in humans;

(*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 effect in humans;

(*c*) the total radiation dose incurred annually by a study subject, including from multiple administrations of the study drug, from significant contaminants or from impurities and from the use of other procedures for the purposes of the study, will be not more than 50 mSv;

(*d*) any concomitant drug used in the study has been assigned a drug identification number under subsection C.01.014.2(1) or, in the case of a concomitant drug that is a new drug, has been issued a notice of compliance under section C.08.004;

(*e*) study subjects shall be at least 18 years old and have legal capacity at the time of the study;

(*f*) female study subjects shall

(i) be confirmed at the outset of the study, on the basis of a pregnancy test, as not being pregnant or state in writing that they are not pregnant, and

(ii) be advised that if they are lactating, they are to suspend lactation for 24 hours after the administration of the study drug; and

(*g*) the study shall not involve more than 30 study subjects.

(2) Despite paragraph (1)(*g*), a study may involve more than 30 study subjects if the sponsor provides the Minister with a scientific rationale for the increase and the Minister approves it.

Research Ethics Board

C.03.306. A research ethics board has all of the following characteristics:

(*a*) its 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;

(*b*) it has 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 the following:

(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,

(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; and

(*c*) it has no affiliations with the sponsor that could compromise its ability to fulfil its principal mandate, or that could be perceived to do so.

Application for Authorization

C.03.307. (1) The sponsor shall submit to the Minister an application for authorization to sell or import a study drug that contains the information set out in subsection (2) as well as sufficient information to demonstrate that all of the following criteria are met:

(*a*) the use of the study drug will not endanger the health of any study subject or other person;

(*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.

(2) The application shall contain 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, expressed in mSv/MBq or rem/mCi;

(*j*) the sponsor's name and civic address, its postal address if different, and its telephone number, fax number and email address;

(*k*) the manufacturer's name and civic address, its postal address if different, and its 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 of 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 at 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 both of the following:

(i) the study will be conducted in accordance with these Regulations, and

(ii) all of the information contained or referred to in the application is complete and accurate and is not false or misleading.

Additional Information

C.03.308. If the information submitted under section C.03.307 is insufficient to enable the Minister to determine whether the sale or importation of the study drug should be authorized, the Minister may, by notice in writing, request the sponsor to provide any additional information that is necessary to make the determination and that is relevant to the study drug, the study or the protocol, by the date specified in the notice.

Authorization

C.03.309. After examining the application and any additional information, the Minister shall authorize the sponsor to sell or import the study drug if she or he determines that the application complies with the requirements of section C.03.307, and shall send a notice of that decision to the sponsor that specifies the study sites in respect of which the sale or importation are authorized.

Notice

C.03.310. The sponsor shall notify the Minister in writing of the day on which the sale or importation of the study drug is intended to start in respect of each study site, not later than 15 days before that day.

Good Clinical Practices

C.03.311. A sponsor shall ensure that each study is conducted in accordance with good clinical practices and that

(*a*) the study is scientifically sound and clearly described in its protocol;

(*b*) the study is conducted, and the study drug is used, in accordance with the protocol and with these Regulations;

(*c*) systems and procedures are implemented that assure the quality of every aspect of the study;

(*d*) at each study site, there is only one qualified investigator;

(*e*) at each study site, medical care and medical decisions, in respect of the study, are under the supervision of the qualified investigator;

(*f*) each individual who is involved in the conduct of the study is qualified by their education, training and experience to perform their respective tasks;

(*g*) before a study subject participates in the study, a copy of their signed consent form is included in the records for the study;

(*h*) the requirements respecting information and records set out in section C.03.315 are met; and

(*i*) the study drug is manufactured, handled and stored in accordance with Division 2, other than sections C.02.019, C.02.025 and C.02.026.

Labelling

C.03.312. Despite any other provision 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,

(vi) the warnings and precautions in respect of the use of the study drug, and

(vii) a list of the possible adverse reactions that are associated with the use of the study drug.

Submission of Information

C.03.313. (1) On the Minister's written request, a sponsor shall submit, within the period specified in the request, information to establish the safety of the study drug if the Minister has reason to believe any of the following:

(*a*) the use of the study drug may endanger the health of a 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 their undertaking made under paragraph C.03.315(3)(*f*); or

(*d*) information submitted in respect of the study drug or study is false or misleading.

(2) The Minister may, by notice in writing, require the sponsor to provide the Minister with any information or records referred to in subsection C.03.315(3) to assess the safety of the study drug or the health of the study subjects or other persons, by the date specified in the notice.

Adverse Reaction Reporting

C.03.314. (1) During the course of a study, the sponsor shall notify the Minister of any serious adverse reaction or serious unexpected adverse reaction that occurs inside or outside Canada, within the following period:

(*a*) if the adverse reaction is fatal or life-threatening, within seven days after becoming aware of it; or

(*b*) if the adverse reaction is not fatal or life-threatening, within 15 days after becoming aware of it.

(2) The sponsor shall, within eight days after having notified the Minister under subsection (1), file with the Minister a complete report in respect of the adverse reaction, including an assessment of the importance and implication of the findings.

(3) Sections C.01.016 to C.01.020 do not apply to study drugs.

Records

C.03.315. (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 these Regulations.

(3) The sponsor shall maintain all of the following records in respect of the use of the study drug in each study:

(*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;

(*g*) for each study site, a copy of the informed consent form; and

(*h*) 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.

Discontinuance of a Study

C.03.316. (1) If a sponsor discontinues a study in its entirety or at a study site, the sponsor shall notify all qualified investigators of the discontinuance as soon as possible in writing, and include in the notice the reasons for the discontinuance and whether the study presented any risks to the health of study subjects or other persons.

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

Suspension

C.03.317. (1) The Minister shall suspend an authorization to sell or import a study drug, in its entirety or in respect of a study site, in any of the following circumstances:

(*a*) information provided by the sponsor under section C.03.307, C.03.308 or C.03.313 proves to be inaccurate or incomplete;

(*b*) the sponsor fails to provide the Minister with sufficient information to establish the safety of the study drug pursuant to a written request under section C.03.313, by the date specified in the request;

(*c*) the sponsor fails to notify the Minister of an adverse reaction or file a report in respect of an adverse reaction in accordance with section C.03.314; or

(*d*) the sponsor contravenes a provision of these Regulations or any provision of the Act in relation to the study drug.

(2) In determining whether to suspend an authorization in its entirety or in respect of a study site, the Minister shall consider whether the reason for the suspension affects the study in its entirety or affects only a certain study site.

(3) Before suspending an authorization, the Minister shall send the sponsor a notice that

(*a*) specifies whether the suspension is of the study authorization in its entirety or in respect of a study site and sets out the reasons for the proposed suspension and the effective date;

(*b*) if applicable, specifies the corrective action that the sponsor must take and the period within which it must be taken; and

(*c*) gives the sponsor a reasonable opportunity to be heard in writing concerning the proposed suspension.

(4) Despite subsection (3), the Minister shall immediately suspend an authorization if she or he has reason to believe that it is necessary to do so to prevent injury to the health of a study subject or any other person.

(5) When the Minister suspends an authorization under subsection (4), the Minister must send the sponsor a notice that

(*a*) sets out the reasons for the suspension;

(*b*) if applicable, specifies the corrective action that the sponsor must take and the period within which it must be taken; and

(*c*) gives the sponsor a reasonable opportunity to be heard in writing concerning the suspension.

Reinstatement

C.03.318 (1) Subject to subsection (2), the Minister shall reinstate the authorization if the sponsor provides the Minister with sufficient evidence to establish that the study does not present a risk of injury to the health of study subjects or other persons, within the following periods:

(*a*) in the case of a suspension under subsection C.03.317(1), 30 days after the day on which the suspension is effective; or

(*b*) in the case of a suspension under subsection C.03.317(4), the period specified in the notice sent under subsection C.03.317(5).

(2) If the Minister does not reinstate any part of an authorization that was suspended, the Minister shall amend the authorization to remove that part.

Cancellation

C.03.319. (1) The Minister shall cancel an authorization, in its entirety or in respect of a study site, in either of the following circumstances:

(*a*) the study is discontinued in its entirety or at that study site by the sponsor under section C.03.316; or

(*b*) the sponsor fails to provide the Minister with the evidence required by subsection C.03.318(1) within the specified period.

(2) When the Minister cancels all or part of an authorization, she or he shall send the sponsor a notice that sets out the reasons for the cancellation and the effective date.

COMING INTO FORCE

6. These Regulations come into force six months after the day on which they are published in the *Canada Gazette*, Part II.

REGULATORY IMPACT ANALYSIS STATEMENT

(This statement is not part of the Regulations.)

Executive Summary

Issue: Health Canada recognizes that basic clinical research using positron-emitting radiopharmaceuticals (PERs) is generally considered safe when PERs with known safety profiles are administered in relatively low doses. Currently, the clinical trial regulations in Part C, Division 5 of the *Food and Drug Regulations* (the Regulations) apply to basic clinical research studies, requiring that a clinical trial application (CTA) be submitted for each study. Both Health Canada and PERs researchers agree that the CTA framework imposes a greater degree of regulatory oversight than necessary, considering the low potential for harm and low level of uncertainty associated with the majority of PERs research studies.

Description: This regulatory amendment introduces a simplified application process for PERs basic clinical research studies that meet the specified inclusion criteria. The new regulations include provisions respecting the submission of an application, good clinical practices, good manufacturing practices, labelling, record-keeping and adverse reaction reporting. Miscellaneous amendments are also being made to update the wording of the Regulations for consistency with the *Radiation Protection Regulations* and to correct an error that was introduced in the Regulations in the past.

Cost-benefit statement: It is estimated that these amendments will lower the costs associated with conducting PERs basic clinical research in Canada by $2.77M annually, and lead to a better understanding of certain diseases and health conditions. Facilitating research for PERs researchers in Canadian institutions should lead to improved access to this technology for routine diagnostic and treatment purposes.

Business and consumer impacts: These amendments will reduce the complexity of the application process, resulting in a lower cost of conducting basic research. Additionally, under the new regulations, sponsors will be required to maintain records for 5 years instead of 25 years as currently required under the clinical trial regulations. No additional costs to consumers or taxpayers are anticipated.

Domestic and international coordination and cooperation: Although these new regulations will be implemented in a different manner than those in place in the United States, the science-based approach to assessing and managing the risk associated with basic research studies will be in line with the US approach. There are no known impacts on international trade agreements or obligations or foreign relations.

Performance measurement and evaluation plan: The main objective of these amendments is to bring in an appropriate level of regulatory oversight for basic research using PERs while still protecting the health and safety of research subjects. As part of its

ongoing performance measurement and evaluation activities, Health Canada will track the number of research studies being conducted with PERs, along with the number of adverse reaction reports received, and changes to the requirements for submission and reporting will be made as needed.

Issue

The Regulations were amended in 2001 to introduce new provisions in Part C, Division 5, for *Drugs for Clinical Trials Involving Human Subjects*. The definition of "clinical trial" in those regulations included basic research activities that were previously not regulated under the investigational new drug provisions, and researchers using PERs for basic research clinical studies involving human subjects found their activities being regulated for the first time.

Background

A PER is a radioactive drug that is comprised of a positron-emitting radionuclide which has been chemically attached to a biologically active molecule. The PER is administered to a patient, typically by injection, and accumulates in different areas of the body depending on the biological activity of the PER used. The radiation emitted from the PER is detected using a positron emission tomography (PET) scanner, producing an image that allows a physician to diagnose or determine the state of a disease.

A PER can also be used for non-diagnostic purposes, providing information about a patient's biological function, such as brain or cardiac activity. Many of these studies are considered to be basic clinical research – studies which differ from clinical trials because they are intended to advance scientific knowledge but not intended to fulfil any immediate diagnostic or therapeutic purpose or to obtain any new knowledge about the effects of the PER itself on study subjects.

The most commonly used PERs have been well-characterized and have a history of safe use in humans. PERs are normally administered in doses so low that no pharmacological effect is observed. Researchers and Health Canada agree that the clinical trial regulations subject many PERs research studies to too much regulatory oversight, considering the relatively low level of risk imposed on study subjects.

Objectives

The purpose of these amendments is to provide a streamlined application process for PERs basic clinical research. The new provisions have been added in Part C, Division 3, and any study meeting the inclusion criteria will now be exempted from the clinical trial requirements in Part C, Division 5. The PERs amendments aim to reduce the amount of paperwork required, for both researchers and Health Canada, and are in line with the recommendations of the Government of Canada's Red Tape Reduction Commission.

Description

This regulatory framework is intended to accommodate the specific needs of PERs basic clinical researchers 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. These regulations outline requirements that must be met before and after the authorization of a basic clinical research study. Any PER used in these studies needs to have an established history of safe use in humans at the proposed radioactive dose, as supported by published literature and/or evidence from valid human or animal studies. Studies involving the concurrent use of a drug that is not a PER and that has not received marketing authorization from Health Canada will have to be submitted as a CTA as per Part C, Division 5 of the Regulations.

Basic clinical research study

A basic clinical research study is an investigation using a PER with a history of safe use in human subjects. A basic clinical research study is intended to obtain:

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

Basic clinical research studies are aimed at advancing scientific knowledge and are not intended to fulfil any immediate diagnostic or therapeutic purposes.

PERs that are used in basic clinical research studies may eventually be authorized for sale in Canada for use in diagnosing and treating diseases such as cancer and cardiovascular diseases, but the research study in question is not meant to diagnose or treat the study subjects.

The clinical trial regulations will continue to apply to clinical studies that fall outside the scope defined above – specifically, those studies intended to:

- discover or verify the pharmacodynamic effects of the drug;
- identify any adverse events in respect of the drug; or
- ascertain the safety or efficacy of the drug.

Applications for authorization of basic clinical research studies

Prior to beginning a basic clinical research study using a PER, the sponsor will be required to submit an application to Health Canada, along with a brief summary of the study protocol. The application will then be reviewed by Health Canada to determine whether the study has met the specific requirements outlined in the regulations.

Research Ethics Board (REB) approval

The requirements for the membership of an REB are outlined in the section C.03.304 of the Regulations.

The principal mandate of the REB, which will operate independently of Health Canada, will be to protect the rights, safety and well-being of basic research subjects. To maintain the integrity of the process, members of the REB may not be affiliated with the sponsor of the study being reviewed. The sponsor will be required to seek REB approval prior to filing an application with Health Canada.

Good clinical practices (GCP)

Sponsors of basic clinical research studies using PERs will have to demonstrate that the studies are conducted according to the generally accepted principles of good clinical practice. Specifically:

- The study must be scientifically sound and clearly described in a protocol that has been approved by an REB.
- For a basic clinical research study to be conducted at multiple sites, each site must have one qualified investigator who is be responsible for medical decisions and the medical care of the subjects involved.
- Every individual involved in conducting the study must be qualified by way of education, training and experience to perform his or her respective tasks.
- To protect safety of the study subjects, each subject must be informed of any potential risks associated with participating in the study. A consent form must be signed prior to the subject's participation in the study.
- Finally, the sponsor must ensure that all the record-keeping requirements are met, and that PERs are manufactured, handled and stored in accordance with the applicable Good Manufacturing Practices (GMP) set out in Part C, Division 2 of the Regulations, with the exception of sections C.02.019, C.02.025 and C.02.026, which outline drug product testing and sample retention requirements placed on importers of drugs into Canada.

Good manufacturing practices (GMP)

Health Canada recognizes that study drugs, like clinical trial drugs, are not at the same stage of development as drugs which have a market authorization (a Notice of Compliance). Further guidance on GMPs, based on those in place for clinical trial drugs, will be provided to stakeholders by Health Canada.

Labelling

The sponsor is required to label all PERs used in basic clinical research studies according to the requirements in these regulations.

The label of the PERs is to include the following information:

(a) the unique batch number for the study drug
(b) the radiation warning symbol set out in Schedule 3 of the *Radiation Protection Regulations* and the words "RAYONNEMENT - DANGER – RADIATION";

The PER is required to have a package insert providing the following information:

(a) a statement indicating that the study drug is to be used only under the supervision of a qualified investigator;
(b) the chemical or generic name of the study drug;
(c) the name and address of the manufacturer;
(d) the name and address of the sponsor;
(e) the protocol code or identification,
(f) the warnings and precautions in respect of the study drug,
(g) the adverse reactions, if any, associated with the study drug.

Records

The sponsor must keep the records related to the basic clinical research study in a manner that allows for verification during an inspection. Because PERs used in basic research are administered in non-pharmacological doses and at relatively low radiation doses, they are not likely to cause a delayed or long-term adverse reaction, so the required period for records retention is five years for PERs research studies, compared to the previously required twenty-five year period under the clinical trial regulations.

Additionally, the sponsor will retain a letter of undertaking, signed and dated by the qualified investigator prior to the commencement of their responsibilities, stating that the qualified investigator will conduct the basic clinical research study in accordance with GCP. The qualified investigator must further commit to inform the study subjects and the REB of the termination of a basic clinical research study when the reason for discontinuance is related to the health or safety of study subjects.

Notice of adverse reactions

Because the rate of adverse reactions to PERs used in the manner outlined in these regulations is expected to be very low, any adverse reaction would be deemed unexpected and would have to be reported to Health Canada. In the event of a serious adverse reaction leading to a fatality or life threatening condition, the sponsor must notify the Minister within 7 days after becoming aware of the information. For an adverse reaction that did not result in death or was not considered life threatening, the sponsor is required to notify the Minister within 15 days after becoming aware of the information.

Within 8 days after having notified the Minister of a serious adverse reaction, the sponsor must submit a complete report of the reaction, including an assessment of the importance and implication of the findings made.

Miscellaneous amendments

Miscellaneous amendments have also been made to update the wording of the Regulations for consistency with the *Radiation Protection Regulations* and to correct an error that was introduced in the Regulations in the past, as follows:

1) The Canadian Nuclear Safety Commission (CNSC), the federal authority regulating the use of nuclear energy and materials to protect health, safety, security and the environment, developed the *Radiation Protection Regulations* in 2000, which replaced the *Atomic Energy Control Regulations*. As a result, the references in subparagraph C.03.202(1)(b)(vi) and paragraph C.03.203(1)(f) of the *Regulations* have now been updated to bring them in line with the wording used by the CNSC; and

2) The reference to item 7 of Schedule B to the *Food and Drugs Act* (the Act) in subsections C.03.204(1) and (2) of the *Regulations* is replaced by a reference to item 8 of Schedule B to the Act to correct an error that was introduced earlier.

Regulatory and Non-Regulatory Options Considered

The options outlined below were considered in the development of this new regulatory framework:

1. Keep basic research under clinical trial regulations

The situation in which researchers had to file a CTA for every basic clinical research study involving a PER was not deemed to be a viable option. Both Health Canada and external stakeholders agreed that the level of detail required for a CTA was not appropriate for basic clinical research studies with PERs. By regulating basic research studies in a manner proportionate to the level of risk involved, unnecessary paperwork burden will be eliminated, and researchers will be able to focus on the advancement of science.

2. Independent body to review PERs basic clinical research applications

In the United States, regulations require that each institution have a Radioactive Drug Research Committee, which reviews and approves proposed research studies involving radioactive drugs in humans. The Food and Drug Administration (FDA) appoints members of these committees. The main advantage to this approach is that the oversight of basic clinical research studies is delegated to a research committee within the institution, thus decreasing the burden on the regulatory body in the assessment of these lower-risk activities.

After consulting with stakeholders, it was decided that the regulatory approach used by the FDA could not work in Canada. Due to the small number of qualified specialists in this area, it would be difficult to form a review committee that is not, in some way, associated with the proposed basic clinical research study being reviewed. In addition,

having a local committee of PERs experts review and give final approval to basic clinical research studies would have added to the administrative burden on the limited number of researchers in this field, something that Health Canada was trying to reduce.

3. No Regulation of Basic Clinical Research using PERs

Prior to September 2001, when the current clinical trial regulations came into effect, most PERs used in basic clinical research studies would have been classified as Investigational New Drugs (IND) if the PER were shipped off-site to another facility or if the sponsor was a private clinic. However, if the PER had been manufactured for on-site use, then an IND submission would not have been required because it would have been considered practice of pharmacy (compounding) / practice of medicine. Because of this history, most stakeholders believed that any sort of regulation of studies involving PERs was unnecessary.

In recent years, many stakeholders had come to agree that a certain level of regulation is prudent. The rationale for regulating these basic clinical research studies is that PERs are drugs as defined in the Act, and there are certain risk factors involved in the administration of any drug to human subjects. Drugs, which have not been evaluated in terms of quality, safety and efficacy, may place human subjects at unknown risk. Although commonly used PERs have an excellent safety record, PERs are not always free of adverse reactions. The new regulations balance the need to protect the health and safety of study subjects with the well-accepted safety record of these of drugs.

4. Introduction of a new regulatory framework for the use of PERs for in basic clinical research studies

The new regulatory framework takes into account:

- the known safety profiles of commonly used PERs and their unique characteristics;
- the assessment and management of the risk to which human research subjects are exposed;
- the size and nature of the affected basic research community;
- the existence of established infrastructure associated with basic clinical research studies with PERs and the costs of maintaining such infrastructure;
- the potential for continued scientific advancements through the use of PERs in basic research studies in the future;
- and the models of review used by regulatory authorities from other countries.

The simplified application process for PERs for basic clinical research takes into consideration both the concerns of researchers and the responsibility that lies with Health Canada as the regulator of drugs.

After consideration of the above proposals, Option 4 was chosen as the preferred alternative.

Benefits and Costs

The chosen option will result in the following benefits and costs. They are presented below according to sector:

Sponsors

Benefits

The new regulatory framework encourages scientists in the field to continue their research in Canada by decreasing the regulatory burden placed on them. These amendments will facilitate scientific research, which may lead to advances in diagnosing and treating diseases such as Alzheimer's disease, Parkinson's disease and cancer. A PER studied in a basic research study may one day become an invaluable diagnostic tool in detecting molecular changes in human biochemistry or physiology in diseases, which are pre-symptomatic, thereby leading to prevention of and early intervention in certain diseases.

The expertise required to navigate the present CTA process may have required the sponsor to hire a contract research organization or a regulatory affairs consultant. These amendments will reduce the complexity of the application process, reducing the amount of supporting information required. This should result in decreased costs to sponsors, with an estimated total savings of $2.77M each year for PERs researchers across Canada.

Under the new regulations, the paperwork burden is being reduced for sponsors, but the risks to study subjects are still being managed. Record-keeping requirements will be brought in line with the actual risks posed to study subjects, with a reduction in the record retention period from 25 years under the clinical trial provisions to 5 years in the new framework.

Costs

Sponsors are not expected to incur any additional costs as a result of these new regulations.

Regulator

Benefits

The resources needed to review a streamlined application for a basic clinical research study will be decreased compared to the resources required to process a CTA.

Costs

There are no additional costs to government associated with compliance and enforcement because the existing clinical trial audit program in Health Products and Food Branch Inspectorate will continue to apply to PER sites.

Public

Benefits

PET is among the most innovative *in vivo* imaging techniques and is used during the initial diagnostic evaluation of patients to monitor and predict therapeutic effectiveness. Human research studies have demonstrated that using PERs in early PET scanning detects abnormalities in early disease development significantly earlier than other diagnostic tools such as Magnetic Resonance Imaging, Computed Tomography, ultrasound and X-ray examination.

As the medical treatment of diseases shifts to community-based care, PERs are expected to be an invaluable diagnostic and treatment tool that will provide patients with a higher level of healthcare by accessing medical knowledge in a non-invasive manner (as opposed to surgeries), thereby avoiding surgical complications and prolonged hospitalizations. The removal of unnecessary regulatory requirements will allow more basic clinical research studies and will likely improve Canadians' access to PET scans for diagnosis and treatment purposes.

Costs

The public should not incur any additional costs due to these new regulations.

Provincial and territorial governments

Benefits

As medical treatment shifts from inpatient hospital stays to community-based care, more widespread use of PET as a diagnostic tool will allow health professionals to provide a high level of health care for a variety of diseases in a non-surgical, non-invasive manner. The use of PERs might reduce post-surgery complications, prolonged hospitalizations and long recovery periods, thus reducing the financial costs associated with hospitalizations. A strong PER basic research program in a particular institution may accelerate the adoption of PET for diagnostic purposes, thereby allowing some of these benefits to be realized.

Costs

Provincial and territorial governments should not expect to incur any additional costs due to these amendments.

Research ethics boards (REBs)

Benefits

The responsibility of REBs with respect to PERs basic clinical research studies will remain the same as their responsibilities to oversee clinical trials under the clinical trial regulations. The sequence has changed, though, and the REB will now be asked to review and approve the basic clinical research study prior to the sponsor's submission of an application to Health Canada.

Costs

These regulations may result in an increased number of PERs basic clinical research studies conducted which may lead to an increased workload for REBs.

Rationale

The new regulatory framework for PERs basic clinical research studies brings the extent of regulatory oversight to a level that is more appropriate for these low-risk studies. These amendments are intended to lead to lower administrative costs, and the knowledge gained from using PERs as a research tool will result in a greater understanding of certain diseases and health conditions.

No additional costs to the Canadian public are expected.

These regulatory requirements address concerns about over-regulation and bring Canadian regulations in line with those in place in the United States. Fostering an active, robust PERs research community will help ensure that Canadians access to PET technology, which is an important tool in both diagnostics and scientific/medical research.

Because of the significant difference in the size of the PERs research communities in Canada and the United States, complete regulatory harmonization is not be possible, but the new regulations align Canadian requirements with those used by the United States regulator, in terms of both risk- management and extent of regulatory paperwork burden.

Consultation

Prior to pre-publication

From 2002 to 2009, Health Canada consulted with PERs stakeholders a number of times in order to understand and address their concerns respecting the clinical trial regulations. There were two mail-out campaigns to solicit feedback on policy documents, and two working group meetings were held to discuss technical issues around the use of PERs in clinical trials and in research settings. Many provisions within the new regulations were derived from discussions held with PERs stakeholders.

A full description of consultations held prior to 2009 can be found on pages 727-728 of the March 21, 2009, issue of *Canada Gazette*, Part I.

Comment period following pre-publication in March 2009

Following pre-publication of these draft regulations, fourteen stakeholder letters were submitted within the 75-day comment period.

One stakeholder was very supportive of the new framework and commented that the changes would work very well within the institution where his research was conducted.

Ten stakeholders expressed concern about the requirements for the basic research application contained within the regulations. Many stated that the requirements appeared to be as onerous as, if not more so than, those for a CTA. Clarification has been provided to stakeholders, informing them that the simplified application form is a checklist to which the sponsor must attest and that much of the required supporting information need not be submitted to Health Canada.

Eight comments were received expressing concern over the application of GMPs to the manufacture of PERs for basic clinical research studies, citing high costs as a prohibitive barrier to researchers' ability to move into compliance with the existing GMP annex for market-authorized PERs. Health Canada will be issuing a guidance document that outlines modified GMP requirements based on those in place for clinical trial drugs. As is done for all guidance documents under development, stakeholders will have an opportunity to comment on revised GMP requirements prior to the release of the finalized document.

Two stakeholders commented that the CNSC already has guidelines in place for research involving human subjects. Although there are a small number of overlapping requirements, the CNSC framework focuses mainly on the safety of the research subject with respect to radiation exposure, whereas the PERs basic research provisions in the *Food and Drug Regulations* focus on clinical safety and drug quality. The requirements of both frameworks are well aligned so that stakeholders will be able to meet the requirements of both without difficulty.

Ten letters contained comments regarding the limit of thirty study subjects, with stakeholders expressing concerns that, for some studies, a thirty-subject cap would not provide sufficient data for statistically meaningful results. Many studies are adequately powered by a sample size of 30, which is the recommended maximum cited in the United States guidance document on the use of radioactive drugs in human research. Health Canada has addressed stakeholder concerns by adding a provision to allow for larger studies if an acceptable scientific rationale is provided. This requirement is in line with that which is in place in the United States.

Two stakeholders remarked on the extent of the labelling requirements for PERs for basic clinical research. The requirements, based on those in the CTA framework in Part C, Division 5 of the Regulations, have been included in this framework to protect the safety of study subjects involved in the basic research study. After careful consideration of stakeholder concerns, Health Canada opted to keep the labelling provisions in place.

Four stakeholders commented that a PER being used for basic research will not likely have a brand name. The regulations have been changed to address this concern.

Two stakeholders commented that the requirement for the drug to be returned and destroyed upon discontinuation of the study is not applicable to PERs, the handling of which is regulated by the CNSC. The wording of this requirement has been changed.

Two stakeholders raised a concern that, if a study were to be terminated, the requirement for notification of the study subjects would raise unnecessary concern among individuals who most likely would not be affected. This provision was reworded to require notification of subjects only in cases where the study was terminated for safety-related reasons.

Five stakeholders commented about the composition and function of the REB. The requirements for membership of the REB for PERs basic research is based on the provisions in the clinical trial framework in Part C, Division 5, of the regulations. In the new PERs framework, minimal information will actually be submitted for review by Health Canada, so the regulations stipulate that REB approval must be sought prior to the filing of an application with Health Canada. Note that pre-approval by an REB will facilitate efficient review times within Health Canada – it is anticipated that staff should be able to meet the 15-day service standard consistently.

Ten stakeholders expressed concern about the limit of 20 mSv for annual total exposure for study subjects. Researchers stated that this limit would exclude many cancer patients because of the doses previously administered as part of their radiation therapy, and they advocated for a limit of 50 mSv (the annual limit set by CNSC for at-risk workers) for cancer patients. Health Canada's scientists were not convinced of this argument, and their stance on this subject remained unchanged after the initial review of the pre-publication comments.

Five stakeholders expressed concern over the wording of the provisions regarding pregnancy testing of female subjects and exclusion of lactating women from the basic research studies. The wording has been changed to clarify the conditions under which pregnancy testing would be required, and the provision regarding lactation has been amended to bring requirements in line with current scientific knowledge.

Stakeholders submitted other comments respecting other aspects of the new regulatory framework, but those comments that were not addressed above did not require changes to the regulations and will be addressed at the guidance level. As per standard practice for guidance development, Health Canada will provide stakeholders with an opportunity to comment on a draft version prior to the finalization of the document.

Call letter – September 2011

As part of its ongoing stakeholder communications, Health Canada sent a letter to radiopharmaceutical stakeholders to solicit general comments regarding ongoing regulatory projects in September 2011. Two letters were received regarding the changes respecting PERs basic research.

The first stakeholder requested clarification with respect to the function of REBs in the PERs basic research framework. The relevant section of this document was revised to address the comment.

The second letter requested clarification regarding: the use of a PER as a tracer in a clinical trial for another (non-PER) drug; the requirements around adverse reaction reporting; and the GMP requirements for the manufacture of study drugs. These issues did not require changes to the regulations and will be addressed at the guidance level.

Also, following the issuance of this call letter, discussions between Health Canada and several members of an umbrella stakeholder group highlighted some confusion among PERs researchers respecting the interim requirements that were in place during the period of policy development and stakeholder consultation and the changes that would come with the finalization of the new regulatory framework for PERs research. In an attempt to provide clarity, Health Canada produced a Questions and Answers document that was distributed to stakeholder by email in December 2011.

Regulatory workshop for radiopharmaceutical stakeholders – March 2012

Health Canada hosted a workshop in Ottawa for radiopharmaceutical stakeholders on March 8-9, 2012. Health Canada staff gave presentations to participants from the scientific, academic, healthcare and commercial sectors of the radiopharmaceutical community. A variety of topics were covered, including these new regulations for PERs basic clinical research. While a number of different issues were discussed, one main issue dominated the two-day workshop.

The topic of limiting the annual total radiation dose to 20 mSv continued to be at the forefront of researchers' concerns at this meeting. The face-to-face forum provided a good opportunity for a productive exchange of information between the regulator and the regulated stakeholders. In the end, Health Canada agreed that, based on the most recent scientific information available, the 50 mSv/year limit set out in the Radiation Protection Regulations as the maximum allowable radiation dose for nuclear workers would also be a suitable limit for study subjects.

Implementation, Enforcement and Service Standards

These amendments do not alter existing compliance mechanisms under the provisions of the Act and Regulations enforced by the Health Products and Food Branch Inspectorate. Inspections, compliance verification and investigations of basic clinical research studies will be conducted to ensure that GCPs and the applicable GMPs are followed.

Health Canada will aim to process applications for authorization for PERs basic clinical research studies within 15 days of receipt.

Performance Measurement and Evaluation

An evaluation of these regulations will be carried out five years after implementation of the framework.

A central objective of these regulations is to reduce the unnecessary regulatory burden on researchers who conduct basic research using PERs. The regulatory requirements and process which are usually associated with clinical trials have been modified for this specific type of research. Assessment and management of risks to human subjects have remained central in the development of these regulations.

As such, evaluation and performance measures will focus on the safety of the basic clinical research subjects, as well as on evidence that the regulatory burden has been reduced for researchers conducting basic clinical research using PERs. The broader implications of these regulations for PERs basic research in Canada will be considered, including whether or not a reduction in regulatory burden has had the desired effect of supporting and enhancing basic research in Canada.

Measures of research subject safety will be addressed up front through the application process and in the post-approval period through the monitoring of adverse events and inspection reports. Where appropriate, current clinical trial requirements and application review times will be used as a basis for comparison (e.g. estimated 50% reduction in review time for PERs basic research applications as compared with clinical trials). Change in the number of successful PERs basic research applications (over a 3 to 5 year period) would provide an indication of overall impact on researchers, as will feedback from key stakeholders.

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