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Regulations Amending the Food and Drug Regulations (Human Plasma Collected by Plasmapheresis)

Statutory authority

Food and Drugs Act

Sponsoring department

Department of Health

REGULATORY IMPACT ANALYSIS STATEMENT

(*This statement is not part of the Regulations.*)

Description

The current regulatory requirements governing the collection of human plasma by plasmapheresis (the plasmapheresis regulations) in Part C, Division 4, of the *Food and Drug Regulations* have become outdated and no longer reflect current practices due to advances in technology. The proposed regulatory amendments will update the existing regulatory provisions to reflect current methods and practices used to collect human plasma as well as the list of transmissible diseases for which tests must be performed. These regulatory amendments recognize advances in methodology and technology in addition to requiring testing for specified transmissible diseases.

Plasmapheresis is a process by which blood is collected from a donor, the plasma portion is separated out and extracted, and the remaining non-plasma portion is returned to the donor. Plasma may be collected by plasmapheresis for purposes of transfusion, for therapeutic reasons, or for use in the manufacture of plasma products. Plasma collected for use in the manufacture of plasma products is known as "source plasma." The

plasmapheresis regulations apply only to source plasma; they do not apply to plasma collected for transfusion. Source plasma is collected from donors during a plasmapheresis session conducted by a fabricator (i.e. operator of plasmapheresis centres).

Some examples of therapeutic uses of plasma products include the treatment of hemophilia and burn victims, and the prevention of life-threatening infections in immunocompromised or immuno-suppressed individuals.

Plasma products used in the prevention of life-threatening infections in immunocompromised or immunosuppressed individuals are called immune globulins. These plasma products contain specific antibodies. To manufacture these plasma products, specific immunization of a donor is required. Specific immunization involves the administration of an immunogen to a donor with the intention of eliciting an immune response in his or her blood. In doing this, plasma collected from a donor who has been specifically immunized is used to manufacture plasma products containing specific antibodies.

In 1978, Schedule D to the *Food and Drugs Act* was amended to add "human plasma collected by plasmapheresis." At the same time, regulatory requirements regarding human plasma collected by plasmapheresis were added to Part C, Division 4, of the *Food and Drug Regulations*. These regulatory requirements were originally introduced in response to concerns about the quality and safety of plasma and the safety of donors.

The proposed amendments are intended to address the following issues:

— the current practice of collecting source plasma by an automated plasmapheresis process which replaced the manual system in use when the current Regulations were made;

— the need to update transmissible disease testing requirements;

— the need to update donor selection criteria to minimize risks to both the donor and to the source plasma supply;

— the need to clarify the requirements for serious adverse reaction reporting, recalls and records management;

— the need to clarify the requirements for donor suitability; and

— the need to clarify the role of medical professionals in the plasmapheresis process.

New regulatory framework

A brief summary of the elements contained in the proposed Regulations follows.

Informing donor of risks

Before beginning plasmapheresis with a person the fabricator must inform the person of what is involved with plasmapheresis, including the risks to the person's health associated with plasmapheresis and with participating in plasmapheresis more frequently than once every eight weeks and obtain from the person their written informed consent to participate in plasmapheresis in accordance with the applicable laws governing consent.

Similarly, before a person can be specifically immunized, a physician must inform the person of what is involved with specific immunization, including the risks to the person's health associated with specific immunization and with receiving the selected immunogen and obtain from the person their written informed consent to receive the selected immunogen in accordance with the applicable laws governing consent.

Person's suitability

In order to maximize the safety of the donor and the quality and safety of source plasma, a person's suitability to participate in plasmapheresis more frequently than once every eight weeks must be determined by a physician or physician substitute, as defined in the Regulations, based on the person's medical history and a medical examination of the person.

The physician or physician substitute must sign a report indicating that the person is suitable to participate in plasmapheresis more frequently than once every eight weeks.

Specific immunization

If a donor is to receive specific immunization, a physician or physician substitute in the presence of a physician administers the immunogen.

The donor's response to the immunogen must be monitored by the physician to determine if the donor can continue to receive specific immunization. If the donor cannot continue to receive specific immunization, the fabricator can no longer proceed with specific immunization with the donor until a physician determines that the donor can resume specific immunization using the same or another immunogen.

Evaluation before collection

At the beginning of each plasmapheresis session, the fabricator must determine if a donor is suitable to participate in plasmapheresis based on the criteria set out in tables 1 and 2 or other medical reasons justifying such a determination. Tables 1 and 2 set out the criteria that could predispose the donor to harm by participating in plasmapheresis more frequently than once every eight weeks, and the conditions, diseases or infections transmissible by blood or plasma which, if suspected to be present in the donor, would preclude the donor from being able to participate in plasmapheresis. The criteria set out in tables 1 and 2 require the suspension of the donor's participation in plasmapheresis. If the donor is not suitable to participate in plasmapheresis having regard to the criteria set out in table 1, the non-suitability is temporary. If the donor is not suitable to participate in plasmapheresis having regard to the exclusion criteria set out in table 2, the non-suitability is for an indefinite period.

The amendments to the Regulations contain improved donor selection provisions to

maximize both the safety of plasma donors in plasmapheresis sessions and the quality and safety of the source plasma being collected. Certain criteria have been added to address known risk factors associated with new diseases that are or may be transmissible by blood that have emerged since the Regulations were originally published. For example, Health Canada is adding a criteria to exclude donors who present a risk for transmission of HIV and Creutzfeld-Jacob disease or variant Creutzfeld-Jacob disease.

Serum protein electrophoresis

Harmonization with the requirements of the United States was sought throughout the Regulations wherever such harmonization was not viewed as negatively affecting the health and safety of Canadians. In the proposed regulatory amendments, the immunoglobulin composition of a donor's blood must be evaluated by means of a serum or plasma protein electrophoresis test or an equivalent test every four months instead of three months as currently required. This regulatory amendment does not negatively affect the health and safety of plasma donors. The test results must be examined by a physician within 21 days after the sample was taken.

Ongoing review of donor records and suitability

The suitability of a donor to continue to participate in plasmapheresis more frequently than once every eight weeks must be determined every four months by a physician based on the test results and collection records for the donor that have been made or received by the fabricator within the preceding four months.

Manual or automated plasmapheresis

The current Regulations were developed at a time when only a manual process was available for the collection of source plasma. A manual system is one in which whole blood is collected from a donor in multiple bags and centrifuged to separate the plasma from other components, and then the non-plasma components are returned to the donor. In an automated plasmapheresis system, blood is withdrawn from a donor, plasma is separated and extracted using centrifugation, filtration or adsorption, and non-plasma components are returned to the donor by intermittent or continuous flow. The proposed amendments will make the regulatory requirements better suited for automated systems and easier to understand and use, since the Regulations will reflect current practice. In addition, the plasma collection limits will be expressed in terms of the volume of plasma collected rather than in terms of whole blood volume, which correlates better with the performance of an automated collection system.

Plasmapheresis procedures

The person conducting plasmapheresis must be employed or otherwise engaged by the fabricator and qualified by education and by training or experience to perform plasmapheresis.

Plasmapheresis must be conducted using aseptic methods and by using a sterile collection system which is licensed under the *Medical Devices Regulations.* All surfaces intended to come into contact with blood or plasma must be pyrogen free. The skin of the

donor at the site of phlebotomy (incision of a vein) must be free from lesion, rash or other source of infection and cleaned and disinfected so that the source plasma will not be contaminated.

A plasmapheresis session can only be conducted if emergency medical personnel are capable of attending at the session within 10 minutes after being contacted by the fabricator.

In order to maximize the safety of the source plasma being collected, the premises used for donor screening, specific immunization or plasmapheresis must be designed, constructed and maintained in a manner that permits medical information to be communicated in confidence.

Maximum volumes and minimum intervals

The plasma collection limits have been revised and are now expressed in terms of volume of plasma collected according to the donor's weight rather than in terms of whole blood volume, which correlates better with current practices of the establishments that perform plasmapheresis for obtaining source plasma.

Donor safety in plasmapheresis sessions is believed to be influenced by the frequency of plasma donation and the total plasma volume collected over a defined period of time. Publications and scientific evidence currently available to Health Canada are considered insufficient to demonstrate that raising the upper limit of total plasma volume collected by plasmapheresis would be as safe and acceptable for a donor as current limits. However, Health Canada will consider such evidence should it become available.

The fabricator must have written procedures that describe the minimum waiting period for a donor between donations of plasma and between a donation of plasma and a donation of blood or other blood components and written procedures that describe the maximum number of plasma donations a donor may make in a given period.

Anticoagulant solution

During plasmapheresis, the anticoagulant solution that is mixed with the blood collected from the donor must be an anticoagulant solution for which a drug identification number (DIN) has been assigned by Health Canada, indicating the solution is suitable for use in plasmapheresis.

The formulae of the anticoagulant solution used is no longer prescribed by regulations. This change is being made to bring into force consistent requirements applicable to all anticoagulant solutions and allows flexibility when there are future changes to anticoagulant solution formulations.

Preservatives and additives

The addition of a preservative or an additive to source plasma is not permitted.

Transmissible disease testing

The regulatory requirements for transmissible disease testing have been expanded to include new diseases that have emerged since the current Regulations originally came into force. These additional tests are already required as a condition of the establishment licence and are currently being performed by all fabricators.

In addition to hepatitis B virus and syphilis, the requirement for HIV types 1 and 2 and hepatitis C virus testing is stated in the Regulations. The specific types of tests used are not mandated by regulation to allow for future technological improvement. The specific types of tests which can be used will be described in a guidance document.

The test results must be reviewed by a physician. In the case of syphilis, if the sample shows evidence of the disease agent present in the donor's blood or plasma, the fabricator can no longer proceed with plasmapheresis until a subsequent test shows that the donor is not infected with the disease agent that causes syphilis, and a physician determines that the donor can continue to participate in plasmapheresis. The donor must be informed in writing of the test result.

In the case of HIV, hepatitis B and hepatitis C, if the sample shows evidence of the disease agent, the fabricator must label the source plasma with the statement "Caution: Not for Manufacturing Use", the name of the disease agent and the hazard symbol for Biohazardous Material set out in Schedule II to the *Controlled Products Regulations*; segregate and dispose of the source plasma; cancel any further plasmapheresis sessions with the donor; and inform the donor in writing that they are no longer suitable to participate in plasmapheresis.

Containers

Source plasma must be stored in a container that is licensed under the *Medical Devices Regulations* for the purpose of collecting and storing plasma. The container must be made of material that permits visual, electronic or automated inspection of the plasma.

Labelling

Clear labelling requirements have been set out in the regulatory amendments to reduce the potential for errors that can occur when plasma is collected. The individual who is responsible for labelling the plasma collected must at the same time label all samples collected for testing.

Storage and transportation

These amendments include provisions outlining the acceptable storage and transportation conditions of the source plasma. Product handling requirements have also been added in cases when plasma has been exposed to storage and transportation temperature variations.

Records management

A fabricator must use and maintain a record-keeping system structured so that with a donor's personal identifier or with a unique identifier for source plasma, the fabricator can

identify the donor and retrieve sufficient records to permit the traceability and recall of source plasma.

In agreement with the recommendation made by the Commission of Inquiry on the Blood System in Canada (Krever Commission) in its interim report released in 1995, "that hospitals record information pertaining to blood and blood components administered to patients and retain these records indefinitely . . .", all records relating to plasma donors must be kept indefinitely.

A summary of all accidents, errors, serious adverse donor reactions and recalls of source plasma must be maintained.

Notice of serious adverse reaction

The proposed regulatory amendment clarifies the requirements for serious adverse reaction reporting. If a donor experiences a serious adverse reaction, a report of the reaction must be provided to the Minister within 24 hours after the fabricator becomes aware of the reaction in the case of a fatality and within 15 days after the fabricator becomes aware of the reaction in any other cases. In the case of a fatality, if the report was made verbally, a written report must be provided within 24 hours after submitting the verbal report.

Recalls

If the fabricator recalls source plasma for a reason involving product safety, the fabricator must provide the Minister with a written report stating the reason for the recall, the number of units involved and the location from which the units were recalled.

Alternatives

The options outlined below provide an overview of the alternatives that were considered.

Option 1: Leaving the existing Regulations in place (maintain the status quo)

The status quo is considered unacceptable. The current regulatory requirements have become outdated and no longer reflect current practices and advances in technology. For example, the current Regulations address the use of a manual plasmapheresis system only, while an automated system is currently used to extract source plasma for the manufacture of plasma products.

The existing transmissible disease testing requirements no longer reflect current practices, nor are they up to date with the diseases known to be transmissible by blood and blood components that have been identified since the original Regulations were made. While testing for the diseases that are being added is currently required as a condition of the establishment licence and are currently being performed by all fabricators, outlining the transmissible diseases for which tests must be performed in the Regulations will add the force of law. These changes are being made to bring into force consistent testing requirements applicable to all establishments.

The current regulatory requirements are not sufficiently clear with respect to the responsibilities of fabricators in serious adverse reaction reporting and records management. The requirements for donor medical suitability as well as the role of medical professionals in the plasmapheresis process need clarification.

The enforcement of the current Regulations is problematic for Health Canada, since the Regulations were not designed with the current practices specifically in mind. The proposed amendments will clarify the requirements from an enforcement perspective for both regulatees and Health Canada's inspectors.

Option 2: Wait for the new regulatory framework for blood and blood components and develop plasmapheresis amendments concurrently

Health Canada is currently working on the development of a regulatory framework for blood and blood components. The renewal of the blood regulatory framework includes an assessment of the current regulatory framework pertaining to the collection, handling and post market surveillance of whole blood and blood components. The objectives of the new framework include outlining clear and intelligible requirements; allowing for timely updating of the requirements as new technologies/products/issues emerge; and achieving greater harmonization in Canada related to the collection, handling and post market surveillance of whole blood and blood components.

One of the elements of this regulatory framework is the development of safety standards for blood and blood components. The National Standards on Blood and Blood Components were developed following extensive collaboration with experts in the field and government stakeholders. The National Standards are aimed at maintaining and enhancing the quality and safety of blood collection, processing, and transfusion. The National Standards have been published and are available for purchase from the Canadian Standards Association (CSA).

Since work on the renewal of the blood regulatory framework is in the early stages, specific details on the components of the new framework are not available at this time. It is anticipated that the renewal of the regulatory framework for blood and blood components will take longer than the development of these regulatory amendments. Such a delay was considered unacceptable.

The plasmapheresis regulations which apply to human plasma collected for use in the manufacture of plasma products are not incompatible with the National Standards which apply to human plasma collected for the purpose of transfusion.

Option 3: Repealing the existing Regulations

While there has not been a problem with the plasma collection centres in recent times, repealing the Regulations in their entirety was discarded as an option because such an action would run contrary to the recommendations that have been made by the Krever Commission. By repealing the Regulations, Health Canada's ability to enforce any safety requirements regarding plasmapheresis would be compromised. This would also be contrary to the interests of Canadian plasmapheresis centres which are in favour of having Health Canada update the existing Regulations.

The safety of donors participating in plasmapheresis could be undermined without specific provisions limiting the frequency and volumes of plasma collection. In the long term, this could affect the quality of the plasma being collected. In addition, the quality of the source plasma itself could be adversely affected if testing requirements are not mandated.

Option 4: Amend the existing Regulations

Amending the existing Regulations is considered the only acceptable option. The proposed regulatory amendments will update the existing regulatory provisions to reflect current plasmapheresis methods and practices used to collect human plasma as well as the list of transmissible diseases for which tests must be performed. The regulatory amendments address the introduction of new technology for collecting and include requirements for testing for transmissible diseases.

The scope of the existing Regulations will remain the same. They apply to source plasma for use in the manufacture of plasma products. By amending the current Regulations, Health Canada will be able to better fulfill its mandate of protecting the health and safety of Canadians participating in, or benefiting from, plasmapheresis intended for the collection of source plasma for use in the manufacture of plasma products.

Benefits and costs

The proposed amendments are expected to have a positive impact on the health and safety of Canadians. The proposed amendments are also expected to benefit industry and other organizations involved in plasmapheresis by establishing clear regulatory requirements. The benefits of the regulatory proposal are detailed below according to sector.

Donors

The benefit to plasma donors participating in plasmapheresis is the confirmation in regulation of current requirements that must be met by fabricators to protect donors' health and safety. The health and safety of donors is a major concern for Health Canada, since there cannot be a plasma collection system without healthy, dedicated donors.

Patients

The benefit to the patient receiving plasma products manufactured from source plasma collected from a donor pool that is protected by clear regulatory requirements with respect to volume limits, donor safety and transmissible disease testing is that there is a greater likelihood of a safer product when the donor pool is stable and consistent.

Provincial and territorial governments and the health care system

Donor and product safety will be reinforced with clear regulatory requirements for transmissible disease testing and collection volume limits which may lead to fewer serious adverse reactions that require treatment.

Pharmaceutical industry and fractionators ("manufacturers of plasma products")

The pharmaceutical industry and fractionators will benefit from having clear regulatory requirements specifically designed to take into account the technology that is currently being used in plasmapheresis centres and from clear regulatory requirements with respect to donor and product safety requirements for the source plasma.

Operators of plasmapheresis centres ("fabricators")

The proposed amendments will have a positive impact on the operators of plasmapheresis centres in Canada. The proposed amendments are intended to clarify the requirements for the operators of plasmapheresis centres to reflect current plasmapheresis methods and practices. The amendments reflect current practices and do not place any undue burdens on industry. The easing of the periodic testing requirement of donors from every three months to every four months reduces the burden on fabricators without adversely affecting the safety or quality of plasma.

The testing requirement for syphilis which used to be part of the ongoing blood monitoring testing requirements has been included with the other transmissible disease testing requirements for plasma samples collected at the time of donation. This will also reduce the costs for operators of plasmapheresis centres.

The safety of the donors and the quality and safety of plasma products will not be compromised in meeting the needs of plasma fabricators.

Consultation

In 1994, under the Drugs Directorate (now the Therapeutic Products Directorate) "Renewal Process," a Blood Regulatory Renewal Project was launched to enhance the blood regulatory framework. The need to update and harmonize the plasmapheresis Regulations was identified as a sub-project of the Blood Regulatory Renewal Project in April of 1995. The work of analysing the changes needed and wordsmithing the proposed changes took place between June 1995 and November 1996.

In 1997, a set of proposed regulatory amendments were developed and sent for comment to 25 plasma and plasma product manufacturers for a 60-day review and comment period. Nine responses were received. All nine respondents expressed concern over Health Canada's proposal not to increase the maximum allowable volume of plasma collected from a donor in a six-month period.

On April 27, 2002, a Notice of Intent was published in the *Canada Gazette*, Part I, with a 60-day comment period. The following stakeholders were notified directly of the publication: the pharmaceutical industry and associations, deans and registrars of pharmacy, medicine, dentistry and veterinary medicine, provincial and territorial ministries of Health, and plasmapheresis stakeholders. Four responses were received. Comments can be summarized as follows:

Comment: All of the respondents are eager to have plasmapheresis regulations that reflect the automated process that is currently used rather than the manual process which is specified in the current Regulations. One respondent requested that the current

Regulations governing manual plasmapheresis not be deleted in case a situation arises in which manual process must be done.

> Response: Since the Regulations deal only with plasmapheresis for obtaining source plasma and, currently, no one would use a manual system for such a purpose, the amendments have been written to reflect the new technology. Volume limits have been expressed in terms of plasma collected rather than whole blood so that foreseeable future technological advances will not require the Regulations to be amended.

Comment: All four respondents addressed the issue of upper limit volumes for the collection of plasma from donors. Two of the respondents are in favour of raising the upper limit volumes especially if the limits were harmonized with those of the United States. One respondent was not in favour of doing so. Another respondent expressed no opinion.

> Response: Publications and scientific evidence currently available to Health Canada are considered insufficient to demonstrate that raising the upper limit of total plasma volume collected by plasmapheresis within a six-month period would be as safe and acceptable as the current limits for a donor participating in plasmapheresis. Health Canada remains open-minded about the issue and will review any data submitted in support of raising the volume limits.

Comment: Two of the respondents feel that the current practice of requiring a yearly examination of donors registered in a donor program is an undue burden that does not increase either donor or recipient safety.

> Response: Health Canada considers the annual physical exam a means of protecting the health of donors participating in plasmapheresis.

Comment: Three of the respondents addressed the issue of inadvertent temperature variation during transport, requesting greater clarity in the new Regulations and harmonization with those of the United States.

> Response: The proposed regulatory amendment will provide the clarity requested. Harmonization with the requirements of the United States was sought throughout the Regulations wherever such harmonization was not viewed as negatively affecting the health and safety of Canadians.

A 75-day comment period will follow publication in the *Canada Gazette*, Part I. Stakeholders, including the following, will be notified directly of the publication: the pharmaceutical industry and associations, deans and registrars of pharmacy, medicine, dentistry and veterinary medicine, provincial and territorial ministries of Health, and plasmapheresis stakeholders. All comments received will be taken into consideration in the preparation of the final proposal.

Compliance and enforcement

The proposed amendment does not alter existing compliance provisions under the *Food and Drugs Act*. The current Regulations are enforced through inspections by the Health

Products and Food Branch Inspectorate. This practice will continue under the new Regulations.

Contact

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PROPOSED REGULATORY TEXT

Notice is hereby given that the Governor in Council, pursuant to subsection 30(1) (see footnote a) of the *Food and Drugs Act*, proposes to make the annexed *Regulations Amending the Food and Drug Regulations (Human Plasma Collected by Plasmapheresis).*

Interested persons may make representations with respect to the proposed Regulations within 75 days after the date of publication of this notice. All such representations must cite the *Canada Gazette*, Part I, and the date of publication of this notice, and be addressed to Julie Gervais, Department of Health, Address Locator 0702A, Building 7, Tunney's Pasture, Ottawa, Ontario, K1A 0K9 (tel: (613) 952-4098; fax: (613) 952-5364; e-mail: julie_ gervais@hc-sc.gc.ca).

Persons making representations should identify any of those representations the disclosure of which should be refused under the *Access to Information Act*, in particular under sections 19 and 20 of that Act, and should indicate the reasons why and the period during which the representations should not be disclosed. They should also identify any representations for which there is consent to disclosure for the purposes of that Act.

Ottawa, August 30, 2005

EILEEN BOYD
Assistant Clerk of the Privy Council

REGULATIONS AMENDING THE FOOD AND DRUG REGULATIONS (HUMAN PLASMA COLLECTED BY PLASMAPHERESIS)

AMENDMENT

1. Sections C.04.400 to C.04.428 of the *Food and Drug Regulations* (see footnote 1) **are replaced by the following:**

Interpretation

C.04.400. The following definitions apply in this section and in sections C.04.401 to C.04.424.

"accident" means an unexpected event that is not an error and that could compromise the safety, efficacy or quality of plasma or the safety of a donor or a fabricator's personnel. (*accident*)

"donor" means a person who is a donor according to section C.04.404. (*donneur*)

"error" means a deviation, whether intended or not, from a fabricator's procedures or applicable laws that could compromise the safety, efficacy or quality of plasma or the safety of a donor or a fabricator's personnel. (*manquement*)

"fabricator" means a person who is the holder of an establishment licence issued under these Regulations that authorizes the person to fabricate source plasma. (*manufacturier*)

"personal identifier" means a unique group of letters, numbers or symbols, or any combination of them, that is assigned to a donor by a fabricator. (*identificateur personnel*)

"physician" means a person who is entitled to practise the profession of medicine under the laws of the province where the services are provided. (*médecin*)

"physician substitute" means a person who

(*a*) acts under the general supervision and direction of a physician; and

(*b*) is authorized to provide a service that may be provided by a physician substitute under sections C.04.400 to C.04.424, according to the laws, if any, of the province where the service is provided. (*substitut*)

"plasmapheresis" means a process during which

(*a*) plasma is separated from blood collected from a donor; and

(*b*) red blood cells and formed elements from the blood are returned to the donor. (*plasmaphérèse*)

"plasmapheresis session" means an appointment between a fabricator and a donor during which the fabricator proceeds or intends to proceed with plasmapheresis. (*séance de plasmaphérèse*)

"serious adverse reaction" means an unexpected and undesirable medical occurrence experienced by a donor during or after plasmapheresis or specific immunization that results in any of the following consequences for the donor:

(*a*) admission to a hospital;

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

(*c*) a medical or surgical intervention to preclude a persistent or significant disability

or incapacity;

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

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

"source plasma" means human plasma collected by plasmapheresis that is intended for use in producing a drug for human use. (*plasma destiné au fractionnement*)

"specific immunization" means the administration of an immunogen to a donor with the intention of eliciting an immune response in their blood for the purpose of plasmapheresis. (*immunisation spécifique*)

"unique identifier" means a unique group of letters, numbers or symbols, or any combination of them that is assigned by a fabricator to source plasma collected at a plasmapheresis session or assigned to red blood cells to be used in specific immunization. (*identificateur unique*)

General Prohibition

C.04.401. No person shall

(*a*) sell source plasma unless it has been fabricated, tested, packaged/labelled, stored and transported in accordance with sections C.04.400 to C.04.424; or

(*b*) fabricate source plasma from blood collected from someone who is not a donor.

Fabricator's Responsibility

C.04.402. (1) A fabricator shall ensure that a person who provides services to them in connection with plasmapheresis or specific immunization is qualified by education and by training or experience to provide the services.

(2) The fabricator shall ensure that the premises used for donor screening, specific immunization or plasmapheresis are designed, constructed and maintained in a manner that permits medical information to be communicated in confidence.

Donor Status

C.04.403. (1) A fabricator shall not begin plasmapheresis with a person unless

(*a*) the fabricator has informed the person of what is involved with plasmapheresis, including the risks to the person's health associated with plasmapheresis and with participating in plasmapheresis more frequently than once every eight weeks; and

(*b*) after paragraph (*a*) has been satisfied, the fabricator obtains from the person

(i) a written acknowledgement that the information specified in paragraph (*a*) has been provided to them, and

(ii) in accordance with the applicable laws governing consent, written informed consent to participate in plasmapheresis.

(2) A fabricator shall not begin the specific immunization of a person unless

(*a*) a physician has selected the immunogen to be administered to the person and informed the person of

(i) the name and nature of the selected immunogen,

(ii) the proposed frequency and the maximum number of specific immunization injections the person would receive, and

(iii) what is involved with specific immunization, including the risks to the person's health associated with specific immunization and with receiving the selected immunogen; and

(*b*) after paragraph (*a*) has been satisfied, the fabricator obtains from the person

(i) a written acknowledgement that the information specified in paragraph (*a*) has been provided to them, and

(ii) in accordance with the applicable laws governing consent, written informed consent to receive the selected immunogen.

C.04.404. (1) A physician or physician substitute shall determine a person's suitability to participate in plasmapheresis more frequently than once every eight weeks based on the person's medical history and a medical examination of the person.

(2) If the person is determined to be suitable, the fabricator shall prepare a written report that includes the following information:

(*a*) the fact that the person is suitable to participate in plasmapheresis more frequently than once every eight weeks;

(*b*) the person's name and personal identifier;

(*c*) the name of the fabricator;

(*d*) the name and signature of the physician who makes or supervises the physician substitute making the determination; and

(*e*) the date of the report.

(3) Subject to subsection (4), the person becomes a donor with the fabricator on the date of the report made by the fabricator in respect of the person.

(4) If the person is already a donor with the fabricator on the date of the report, the person retains their status as a donor with the fabricator.

(5) The person loses their status as a donor with the fabricator if

(*a*) the fabricator has not proceeded with plasmapheresis or specific immunization with the donor within 30 days after the date the person became a donor with the fabricator;

(*b*) within the previous 12 months, a physician or physician substitute has not made a determination under subsection (1) in respect of the person; or

(*c*) the person is not suitable to participate in plasmapheresis under subsection (1), under subsection C.04.406(3) or C.04.408(3) or under paragraph C.04.413(4)(*c*).

Specific Immunization

C.04.405. (1) No one other than a physician or physician substitute in the presence of a physician shall administer an immunogen to a donor for the purpose of specific immunization.

(2) A physician shall monitor the donor's response to the immunogen to determine if the donor can continue to receive specific immunization.

(3) If the donor cannot continue to receive specific immunization, the fabricator shall cease to provide it to the donor until a physician determines that the donor can receive specific immunization using the same or another immunogen.

Evaluation Before Collection

C.04.406. (1) At the beginning of each plasmapheresis session, a physician, physician substitute or person who acts under the supervision of a physician shall determine if the donor is suitable to participate in plasmapheresis.

(2) If the donor is temporarily not suitable to participate in plasmapheresis having regard to the criteria set out in Table 1 or any other medical reason justifying a determination of temporary non-suitability, the fabricator shall cancel the session, inform the donor of the reasons why they are not suitable and indicate the date when the donor may continue to participate in plasmapheresis.

(3) If the donor is not suitable to participate in plasmapheresis for an indefinite period having regard to the exclusion criteria set out in Table 2 or for any other medical reason that justifies a determination of indefinite non-suitability, the fabricator shall cancel the session and inform the donor in writing of the reasons why they are not suitable.

TABLE 1

Item	Criteria
1.	Weight of less than 50 kg
2.	Temperature outside of normal limits
3.	Blood pressure above 100 mmHg diastolic or 180 mmHg systolic
4.	Haemoglobin level of less than 125 g/L of blood
5.	Haematocrit value of less than 0.38L/L of blood
6.	Total protein level of less than 60 g/L of blood
7.	Substantial blood loss
8.	Prior donation of plasma or other blood components
9.	Pregnancy
10.	History of medical or surgical procedures
11.	History of convulsions requiring medical treatment
12.	Ability to answer questions compromised by alcohol or drug use
13.	Prior transfusion of blood, blood components or a blood product, or prior transplantation of a cell, tissue or organ other than dura mater
14.	Skin infection at the site of the phlebotomy
15.	Sign or symptom of infection
16.	Risk of HIV infection based on, but not limited to, a history of acupuncture, skin piercing, tattooing, accidental needle-stick injury or occasional sexual relations with a person at risk of having AIDS or HIV infection
17.	Current or past use of medication that poses a risk to a recipient of a product manufactured from source plasma
18.	Receipt of a live attenuated vaccine
19.	Animal bite requiring prophylaxis for rabies or for which the need for post-exposure prophylaxis has not been assessed

TABLE 2

Item	Exclusion Criteria
1.	Abnormal cardiovascular function or serious or chronic cardiovascular disease
2.	Abnormal respiratory function or serious or chronic respiratory disease
3.	Bleeding disorder
4.	Serious disease or medical condition of the liver, kidneys, another organ or of a system or blood
5.	Abnormal serum proteins, including monoclonal or polyclonal gammopathy
6.	Current or past use of medication that poses an ongoing risk to a recipient of a product manufactured from source plasma
7.	History of recurrent fainting associated with the donation of blood or plasma

8.	History, signs or symptoms of injectable drug abuse such as skin punctures, scars or sharing needles to inject drugs
9.	History, signs or symptoms of AIDS or HIV infection
10.	Risk of HIV infection based on established lifestyle or sexual relations
11.	History, signs or symptoms of a chronic or persistent infection or parasitic disease transmissible by blood
12.	History, signs or symptoms of hepatitis, other than hepatitis A
13.	Cancer, other than non-melanoma skin cancer or in-situ cervical cancer.
14.	Risk factor for CJD or variant Creutzfeldt-Jacob disease (vCJD) based on, but not limited to, the receipt of dura mater transplant or a treatment using a human pituitary hormone
15.	Positive test result for any transmissible disease agent

Immunoglobulin Composition

C.04.407. (1) Before beginning plasmapheresis with a donor, a fabricator shall take a blood sample from the donor to determine the immunoglobulin composition of the donor's blood by means of a serum or plasma protein electrophoresis test or an equivalent test.

(2) A blood sample shall be taken within seven days before the donor's first plasmapheresis session at which the fabricator proceeds with plasmapheresis.

(3) If 21 days have elapsed from the taking of the sample without a physician examining the test result, the fabricator can no longer proceed with plasmapheresis with the donor until a physician examines the test result.

(4) If a physician concludes that the immunoglobulin composition of the donor's blood is not within normal limits, the fabricator can no longer proceed with plasmapheresis with the donor until a physician determines that the immunoglobulin composition of the donor's blood is within normal limits.

(5) If the fabricator has not taken a blood sample from the donor as required under subsection (1) for more than four months, the fabricator can no longer proceed with plasmapheresis with the donor until the blood sample is taken from the donor.

On-going Review of Collection Records

C.04.408. (1) A physician shall determine if a donor is suitable to continue to participate in plasmapheresis more frequently than once every eight weeks, based on the test results and collection records for the donor that have been made or received by the fabricator within the preceding four months.

(2) The determination shall be made at least every four months after the person becomes a donor with the fabricator.

(3) If the donor is determined to be not suitable for an indefinite period, the fabricator can

no longer proceed with plasmapheresis with the donor and shall inform the donor in writing of the reasons why they are not suitable.

(4) If the requirement of subsection (2) is not met, the fabricator can no longer proceed with plasmapheresis with the donor until the determination is made.

Plasmapheresis Procedures

C.04.409. A fabricator who conducts a plasmapheresis session shall:

(*a*) use aseptic methods and a sterile collection system licensed under the *Medical Devices Regulations*;

(*b*) ensure that all surfaces intended to come into contact with blood or plasma are pyrogen free;

(*c*) ensure that the donor's skin where the phlebotomy is to be made is

(i) determined to be free from lesion, rash or other source of infection, and

(ii) cleaned and disinfected; and

(*d*) ensure that medical personnel are capable of attending at the session within 10 minutes after being contacted by the fabricator.

Maximum Volumes and Minimum Intervals

C.04.410. (1) A fabricator shall not collect plasma from a donor in a total amount, excluding anticoagulant solution, that exceeds

(*a*) if the donor's body weight is 50 kg or more but less than 68 kg,

(i) 625 mL or 640 g in respect of a single plasmapheresis session, and

(ii) 11.5 L in respect of all plasmapheresis sessions during the preceding six months;

(*b*) if the donor's body weight is 68 kg or more but less than 80 kg,

(i) 750 mL or 770 g in respect of a single plasmapheresis session, and

(ii) 15.5 L in respect of all plasmapheresis sessions during the preceding six months; and

(*c*) if the donor's body weight is 80 kg or more,

(i) 800 mL or 820 g in respect of a single plasmapheresis session, and

(ii) 18.5 L in respect of all plasmapheresis sessions during the preceding six months.

(2) The fabricator shall have written procedures that describe

(*a*) the minimum waiting period for a donor between donations of plasma and between a donation of plasma and a donation of blood or other blood components; and

(*b*) the maximum number of plasma donations a donor may make in a given period.

Anticoagulant Solution

C.04.411. (1) During plasmapheresis, the fabricator shall mix an anticoagulant solution with the blood collected from the donor.

(2) The anticoagulant solution shall have a valid drug identification number under these Regulations that indicates the solution is suitable for use in plasmapheresis.

Source Plasma Samples

C.04.412. (1) During a plasmapheresis session, the fabricator shall take a sample of blood or plasma in a manner that does not contaminate the sample or the source plasma.

(2) When the sample is taken, the fabricator shall clearly and permanently label the sample container with the unique identifier for the source plasma.

(3) The fabricator shall ensure that the person who labels the sample container is the same person who labels the container holding the source plasma under subsection C.04.416(2).

C.04.413. (1) The fabricator shall test a sample taken under section C.04.412 to detect evidence of the following disease agents:

(*a*) HIV types 1 and 2;

(*b*) hepatitis B virus;

(*c*) hepatitis C virus; and

(*d*) syphilis.

(2) The fabricator shall retain the source plasma collected at the plasmapheresis session until the test results have been reviewed by a physician.

(3) In the case of a positive or reactive test result for syphilis, the fabricator

(*a*) can no longer proceed with plasmapheresis with the donor until a subsequent test shows that the donor is not infected with the disease agent that causes syphilis and a physician determines that the donor can continue to participate in plasmapheresis;

(*b*) shall inform the donor in writing of the test result; and

(*c*) shall segregate and dispose of the source plasma.

(4) In the case of a positive or reactive test result for a disease agent mentioned in subsection (1), other than syphilis, the fabricator shall

(*a*) clearly and permanently label the container holding the source plasma collected at the session with

(i) the statement "Caution: Not for Manufacturing Use" or "Précaution : Non destiné à la fabrication",

(ii) the name of the disease agent, and

(iii) the hazard symbol for Biohazardous Infectious Material set out in Schedule II to the *Controlled Products Regulations*;

(*b*) segregate and dispose of the source plasma; and

(*c*) discontinue plasmapheresis with the donor and inform the donor in writing that they are not suitable to participate in plasmapheresis for an indefinite period with supporting reasons.

Preservatives and Additives

C.04.414. No person shall add a preservative or additive to source plasma.

Containers

C.04.415. A fabricator shall place source plasma in a container

(*a*) in respect of which a medical device licence has been issued under the *Medical Devices Regulations* for the purpose of collecting and storing plasma;

(*b*) that permits visual, electronic or automated inspection of the plasma;

(*c*) that has been visually inspected at the plasmapheresis session and found to be intact; and

(*d*) that has not been previously used for any purpose, including holding source plasma from the same donor.

Labelling

C.04.416. (1) Sections C.01.004 and C.04.019 do not apply to source plasma.

(2) A fabricator shall clearly and permanently label the container used to hold source plasma with

(*a*) the unique identifier for the source plasma in the container;

(*b*) the statement "Source Plasma" or "Plasma destiné au fractionnement";

(*c*) the statement "Caution: For Manufacturing Use Only" or "Précaution : À utiliser uniquement pour la fabrication";

(*d*) the quantity of the source plasma;

(*e*) the name and quantity of the anticoagulant added to the source plasma;

(*f*) the collection and expiry date of the source plasma, expressed in an unambiguous format;

(*g*) subject to subsection C.04.413(4), a statement indicating that the source plasma tests negative for the disease agents for HIV types 1 and 2, hepatitis B and hepatitis C;

(*h*) if the source plasma was collected from a donor who has received specific immunization, a statement indicating the immunogen that was used;

(*i*) the name, address and establishment licence number of the fabricator; and

(*j*) a statement indicating that the source plasma must be stored at a temperature of -20°C or colder.

(3) The unique identifier for the source plasma shall be placed on the container at the time of collection.

Storage and Transportation

C.04.417. (1) A fabricator shall store and transport source plasma in an environment designed to maintain a temperature of -20°C or colder.

(2) The fabricator shall ensure that the environment remains consistently at a temperature of -20°C or colder.

(3) If the temperature of the environment is greater than -20°C, the fabricator shall record the following information:

(*a*) the reason for the elevated temperature;

(*b*) the source plasma affected; and

(*c*) the final disposition of the source plasma.

C.04.418. (1) If the temperature of the environment rises to between -20°C and +10°C, the fabricator shall clearly and permanently label the container of the source plasma with the statement "Source Plasma — Salvaged" or "Plasma destiné au fractionnement — recyclé" and shall not sell the plasma for use in manufacturing an injectable drug.

(2) Subsection (1) does not apply if the temperature of the environment rises to between -20°C and -5°C for a single occasion lasting less than 72 hours.

(3) If the temperature of the environment rises above +10°C, the fabricator shall dispose of the source plasma.

C.04.419. (1) A fabricator shall inspect each container of source plasma to determine if the container and its label are intact and if the plasma has been subject to thawing.

(2) The fabricator shall dispose of the source plasma if the inspection shows that

(*a*) the container is defective or damaged to the extent that it does not provide protection against external factors that could result in deterioration or contamination of the plasma;

(*b*) any information referred to in paragraphs C.04.416(2)(*a*) to (*i*) is missing or illegible; or

(*c*) the plasma has been subject to thawing.

Records Management

C.04.420. (1) A fabricator shall use and maintain a record-keeping system according to which the fabricator shall

(*a*) assign a personal identifier to each donor;

(*b*) retain on the donor's file a photograph of the donor or some other equally effective means of identification; and

(*c*) assign a unique identifier to the source plasma collected by the fabricator at each plasmapheresis session.

(2) The system shall be structured so that a fabricator may, based on a donor's personal identifier or a unique identifier for source plasma, identify the donor and retrieve sufficient records to permit the traceability and recall of source plasma.

(3) The fabricator shall retain the records referred to in subsection (2) indefinitely.

C.04.421. (1) For each person determined suitable under subsection C.04.404(1), the fabricator shall keep:

(*a*) the original or a copy of the person's acknowledgement and consent under paragraphs C.04.403(1)(*b*) and C.04.403(2)(*b*), if any;

(*b*) the original or a copy of any determinations, examinations, test results and reports made under sections C.04.400 to C.04.424;

(*c*) for each specific immunization given by the fabricator to the person, a record indicating

(i) the date and location of the immunization,

(ii) the physician present and the physician substitute, if any, who administered the immunogen, and

(iii) for the immunogen injected, its name and manufacturer's name, the quantity and expiry date and either the immunogen's lot number and drug identification number or, if the immunogen is red blood cells, its unique identifier;

(*d*) for each plasmapheresis session held by the fabricator for the person, a record indicating

(i) the date and location of the session,

(ii) the volume of source plasma collected,

(iii) the unique identifier for the source plasma,

(iv) the total volume of red blood cells collected that were not returned to the person, including the volume of red blood cells collected during sampling,

(v) for the anticoagulant solution used, its name, its manufacturer's name and its lot number and drug identification number, and

(vi) for the container used, the manufacturer's name and the container's lot number and expiry date.

(2) The fabricator shall maintain a summary of all accidents, errors, serious adverse reactions and recalls of source plasma involving the fabricator.

(3) The fabricator shall maintain temperature records made under subsections C.04.417(2) and (3).

Information to the Minister

C.04.422. (1) If a donor experiences a serious adverse reaction, the fabricator shall provide a report of the reaction to the Minister

(*a*) within 24 hours after the fabricator becomes aware of the occurrence, in the case of a fatality; and

(*b*) within 15 days after the fabricator becomes aware of the occurrence, in any other case.

(2) In the case of a verbal report made under subsection (1), the fabricator shall submit a written report of the serious adverse reaction to the Minister within 24 hours after submitting the verbal report.

(3) The written report shall include a description of the serious adverse reaction and any steps taken to address it.

C.04.423. If a fabricator recalls source plasma for a reason involving product safety, the fabricator shall provide the Minister with a written report stating the reason for the recall, the number of units involved and the location from which the units were recalled.

C.04.424. In order to prevent injury to the health and safety of donors and recipients of products manufactured from source plasma, a fabricator shall, on request, provide the Minister with a copy of any record pertaining to plasmapheresis, specific immunization or source plasma that is required by sections C.04.400 to C.04.423 to be kept by the fabricator.

COMING INTO FORCE

2. These Regulations come into force on the day on which they are registered.

[36-1-o]

Footnote a

S.C. 1999, c. 33, s. 347

Footnote 1

C.R.C., c. 870

NOTICE:
The format of the electronic version of this issue of the Canada Gazette was modified in order to be compatible with hypertext language (HTML). Its content is very similar except for the footnotes, the symbols and the tables.

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Important Notices

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