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THERAPEUTIC PRODUCTS PROGRAMME

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Programme des produits thérapeutiques

NOTRE MISSION : Faire en sorte que les médicaments, les matériels médicaux et les autres produits thérapeutiques disponibles au Canada soient sûrs, efficaces et de haute qualité.

HEALTH CANADA DIRECTIVE

TECHNICAL REQUIREMENTS FOR THERAPEUTIC DONOR INSEMINATION

July 2000

Canada

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PREFACE

The Health Canada Directive entitled ***Technical Requirements for Therapeutic Donor Insemination*** is intended to minimize the risk of disease transmission via donated semen. Clauses 2 to 5 of this Directive, entitled "Exclusions", "Work-Up", "Repeat Screening & Quarantine" and "Microbiology", specify the minimum requirements for screening and testing donors of semen for use in assisted conception.

In this Directive, the words "shall" or "must" indicate a requirement. The term "should" indicates a recommendation. Notes accompanying clauses do not include mandatory or alternative requirements. The purpose of these notes is to set out explanatory or informative material.

A. LIST OF ABBREVIATIONS

AIDS	Acquired Immuno-Deficiency Syndrome
CJD	Creutzfeldt-Jakob Disease
CMV	Cytomegalovirus
DI	Donor Insemination
FTA-ABS	Fluorescent Treponemal Antibody Absorption Test
HBcAg	Hepatitis B Core Antigen
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTLV	Human T-cell Lymphotropic Virus
IgG	Immune Globulin G
IgM	Immune Globulin M
MHA-TP	Microhemagglutination Assay for *Treponema pallidum*
SOPs	Standard Operating Procedures
TDI	Therapeutic Donor Insemination

B. DEFINITIONS

Canadian STD Guidelines: The 1998 Edition of the Canadian Sexually Transmitted Disease (STD) Guidelines (ISBN- O-662-27208-0; website availability at http://www.hc-sc.gc.ca/hpb/lcdc/bah), as amended from time to time.

CFAS 1996 Guidelines: The Canadian Fertility and Andrology Society 1996 Guidelines for Therapeutic Donor Insemination.

> **Note: The *Guidelines for Therapeutic Donor Insemination,* as amended from time to time, published by the Canadian Fertility and Andrology Society, Montreal, were referenced in the *Processing and Distribution of Semen for Assisted Conception Regulations,* made under the *Food and Drugs Act.***

Repeatedly Reactive: A blood sample which is reactive on initial testing, and is still reactive in at least one of two duplicate samples when the same test is repeated using the same blood sample.

Semen Fully Processed Prior to March 14, 2000: Semen in respect of which the measures referred to under the following headings have been taken prior to March 14, 2000:

(a) "Exclusions", "Work-Up", "Repeat Screening & Quarantine" and "Semen Microbiology" of the CFAS 1996 Guidelines; or
(b) "Exclusions", "Work-Up", "Repeat Screening & Quarantine" and "Microbiology" of this Directive.

C. SEMEN DONOR RECRUITMENT, SCREENING AND TESTING

1. DONOR SELECTION - GENERAL

1.1 Recruitment

Any healthy men not excluded on the basis of the criteria set out under the heading "Exclusions" in Clause 2 are eligible to donate semen.

1.2 Donor Screening Procedures

Each semen bank or fertility clinic shall adhere to donor screening procedures as specified in the facility's Standard Operating Procedures (SOPs) and this Directive.

1.3 Medical Records

Medical records regarding the donor should be kept indefinitely.

2. EXCLUSIONS

2.1 Exclusion Criteria

The exclusion criteria shall include the following:

(c) Employment by the facility or having a family member employed by the facility;

(d) Age greater than 40 years;

(e) Indications of high risk for the Human Immunodeficiency Virus (HIV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), or Human T-cell Lymphotropic Virus (HTLV), including:

i. men who have had sex with another man, even once, since 1977;
ii. persons who report intravenous, intramuscular, or subcutaneous injection of drugs that are not prescribed by a licensed physician for medical purposes;
iii. persons who report tattoos or body piercing involving non-sterile skin penetration in the preceding 12 months;

iv. persons with hemophilia or related clotting disorder who have received human derived clotting factor concentrates;

v. persons who have engaged in sex in exchange for money or drugs at anytime since 1977;

vi. persons who have had sex in the preceding 12 months with any person described in item (c)(i) through (c)(v) above;

vii. persons who have been exposed to known or suspected HIV infected blood or body fluids through percutaneous inoculation or through contact with an open wound, non-intact skin, or mucous membrane;

viii. persons who cannot be tested for infectious disease agents because of refusal, inadequate blood sample, or other reasons;

ix. persons with a history of repeatedly reactive screening for antibody to HIV-1 or HIV-2, Hepatitis B surface antigen (HBsAg), antibody to Hepatitis B core (HBc) antigen, antibody to HCV, or antibody to HTLV-I or HTLV-II, regardless of the results of supplemental assays;

x. persons whose history, physical examination, medical records, or pathology report reveal other evidence of infection or high-risk behaviours, such as:

(1) diagnosis with Acquired Immuno-Deficiency Syndrome (AIDS);
(2) unexplained weight-loss;
(3) night sweats;
(4) blue or purple spots on the skin or mucous membranes typical of Kaposi's Sarcoma;
(5) unexplained lymphadenopathy lasting more than 1 month;
(6) unexplained temperature greater than 38.6 ºC (100.5 F) for more than 10 days;
(7) unexplained persistent diarrhea; or
(8) needle tracks or other signs of parenteral drug use;

xi. persons who have, or have had, sex with a person known to have HIV, HBV, HCV, or HTLV infection, or who is at high risk for such infection;

xii. persons who are at risk of having acquired HIV from geographic regions which are endemic for HIV strains that are not detectable by current screening tests (these individuals may be reconsidered once tests to detect the variant strains become available);

Note: Information regarding geographic regions which are endemic for HIV strains that are not detectable by current screening tests is available at Health Canada.

xiii. persons with active viral hepatitis;

xiv. persons who have received, or whose sexual partners have received blood, blood components, blood products or other human tissues in the preceding 12 months;

xv. persons who have been exposed to blood or body fluids through percutaneous inoculation or through contact with an open wound, non-intact skin, or mucous membrane in the preceding 12 months;
xvi. persons who have been excluded permanently from donating blood;
xvii. persons who have used intra-nasal cocaine in the preceding 12 months;

Note: The criteria outlined in clause 2.1(c) have been excerpted from the Guidelines for Preventing Transmission of Human Immunodeficiency Virus Through Transplantation of Human Tissues and Organs - Morbidity and Mortality Weekly Report (MMWR), U.S. Center for Disease Control: 43; RR8, May 29, 1994, and modified to conform with the exclusion criteria for Canadian blood donors.

(d) Sexually transmitted disease in the preceding 12 months;

(e) Sexual encounter in the preceding 12 months with someone whose sexual background the potential donor is unsure of;

(f) Urethral discharge, genital warts, or genital ulcers at the time of donation;

(g) History of alcoholism;

(h) Diagnosis with Creutzfeldt-Jakob Disease (CJD) or a first degree family member with a history of CJD;

(i) Receipt of human pituitary-derived growth hormone or dura mater;

(j) Spongiform encephalopathy or prion disease;

(k) Viral encephalitis or encephalitis of unknown origin; or

(l) Any major systemic diseases, including systemic malignancies.

2.2 Semen Processed Prior to March 14, 2000

For semen processed prior to March 14, 2000, only the measures set out in Clause 6 apply.

3. WORK-UP

3.1 Suitability of Donor

The suitability of a specific individual for semen donation shall be documented and based on medical, sexual and social history, clinical status, physical examination, and laboratory test results.

3.2 Questionnaire

The Medical Director or a Physician Designated by the Medical Director shall be responsible for the preparation of medical, social and sexual history questionnaires.

3.3 Donor Selection Process

3.3.1 Donor Information Sheet

A donor information sheet should be provided to the donor.

3.3.2 Required Elements

(a) The donor selection process shall include the following:

i. staff designated by the Medical Director of the semen bank or fertility clinic shall have initial discussions with the potential donor. The discussion shall emphasize the importance of the Donor Insemination (DI) Programmes and the donors' responsibilities towards them;

ii. a donor consent form shall be completed by the donor; and

iii. a donor medical questionnaire must be completed.

(b) A preliminary semen evaluation, including a cryopreservation test, shall be conducted.

(c) A medical interview shall be conducted, and shall include:

i. a physical examination;

ii. a medical history; and

iii. laboratory tests, including the infectious disease tests specified in Clauses 3.5.2 and 3.5.4. The infectious disease tests specified in Clause 3.5.3 should also be performed.

(d) The acceptance of a donor shall be decided by the Medical Director or a Physician Designated by the Medical Director.

(e) If a donor is accepted, a unique identifier shall be assigned to that donor. The semen bank or fertility clinic shall be responsible for ensuring donor confidentiality.

3.4 Documentation

Documentation in respect of each donor shall include the following:

(a) Name of the donor;
(b) Unique identifier of the donor;
(c) Address of the donor;
(d) Donor's date of birth;
(e) Completed medical questionnaire;
(f) Completed donor consent form;
(g) Medical records;
(h) Completed physical examination results;
(i) Laboratory test results; and
(j) Name and signature of the Medical Director or a Physician Designated by the Medical Director, who reviewed, examined and approved the semen donor.

3.5 Initial Testing

3.5.1 General

3.5.1.1 Infectious Disease Testing

(a) The Standard Operating Procedures (SOPs) of every semen bank or fertility clinic shall describe all infectious disease tests that must be performed.

(b) Testing shall be performed by a laboratory that meets federal accreditation requirements, or the accreditation requirements of the province or territory in which the laboratory is located, or in the case of imported semen, by a laboratory that meets a recognized equivalent accreditation requirement.

(c) The serological tests specified in Clause 3.5.2 shall be performed on a blood specimen obtained from the semen donor:

i. with donor screening test kits approved or licensed under the Canadian *Medical Devices Regulations,* if such test kits are available through the accredited laboratory referred to in Clause 3.5.1.1(b), or

ii. with diagnostic test kits that have been approved or licensed under the Canadian *Medical Devices Regulations,* in any other case.

Note: It is appropriate risk management to use diagnostic test kits on a temporary basis until donor screening tests are available and licensed under the Canadian *Medical Devices Regulations*.

(d) The serological tests specified in Clause 3.5.3 should be performed on a blood specimen obtained from the semen donor:

i. with donor screening test kits approved or licensed under the Canadian *Medical Devices Regulations,* if such test kits are available through the accredited laboratory referred to in Clause 3.5.1.1(b), or

ii. with diagnostic test kits that have been approved or licenced under the Canadian *Medical Devices Regulations,* in any other case.

(e) Microbiological testing for *Chlamydia trachomatis and Neisseria gonorrhoeae* shall be performed with test kits that have been approved or licenced under the Canadian *Medical Devices Regulations* for the specimen being tested, if such test kits are available through the accredited laboratory specified in Clause 3.5.1.1 (b). The manufacturers' instructions for the performance and interpretation of their tests and the manufacturers' requirements for specimens shall be followed.

(f) If microbiological testing for *Chlamydia trachomatis and Neisseria gonorrhoeae* is performed using a test or method developed by the accredited laboratory specified in Clause 3.5.1.1(b), the laboratory must have validation data to support the use of the test or method for the intended application.

(g) Donors who test positive for any of the infectious disease markers or infectious agents listed in Clauses 3.5.2, 3.5.4, 4.1.1, 4.2.2 (b), 5.1 and 5.2 must be rejected.

3.5.1.2 Notification Requirement

Positive results for the serological and microbiological tests specified in Clauses 3.5, 4 and 5 shall be immediately reported in writing to the donor by the semen bank or fertility clinic.

Note: Canadian semen processors should also report positive serological and microbiological test results to the Public Health Authority as required in the notifiable diseases reporting process under the applicable *Public Health Act and Regulations* of each province and territory.

3.5.2 Minimum Serological Testing

Minimum serological testing shall include tests for:

(a) Antibody to HIV-1 and 2;
(b) Antibody to HCV;
(c) Hepatitis B surface antigen (HBsAg);
(d) Antibody to Hepatitis B core antigen (IgG anti-HBcAg);
(e) Antibody to HTLV-I and HTLV-II; and
(f) *Treponema pallidum* (syphilis)
    i. non-treponemal test; and
    ii. treponemal-specific test (FTA-ABS or MHA-TP).

Note: Additional information on the laboratory diagnosis of syphilis can be found in the Canadian STD Guidelines

3.5.3 Additional Serological Testing

Additional serological testing should include tests for Cytomegalovirus (CMV) IgM & IgG.

Note: IgM positive donors should be deferred from donating semen until they become IgM negative. CMV IgG positive donors should also be deferred if any additional testing shows the presence of active infection at the time of donation. CMV IgG positive donors should be used only for CMV seropositive recipients. IgG negative donors may be used for CMV seropositive or seronegative recipients.

3.5.4 Minimum Microbiological Testing

Minimum microbiological testing shall include:

(a) A test for *Chlamydia trachomatis* using a nucleic acid amplification test on urine, urethral or semen specimens;

(b) A test for *Neisseria gonorrhoeae* using:

i. urethral or semen cultures*;* or

ii. a nucleic acid amplification test on urine, urethral or semen specimens; and

Note: Urine and urethral specimens for microbiological testing should be collected and transported as described in the Canadian STD Guidelines.

For the purposes of donor counseling and treatment, a positive nucleic acid amplification test result should be confirmed using a different set of primers to rule out false positive results.

Additional information on the laboratory diagnosis of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* infections can be found in the Canadian STD Guidelines.

(c) A general semen culture and sensitivity evaluation.

Note: A positive test consists of any organisms not considered normal flora.

3.6 Rh Status

The donor's Rh Status shall be determined at either the initial testing stage, or at any time before the semen is released for distribution.

Note: In the case of an Rh negative recipient an Rh negative donor should be used whenever possible.

3.7 Archived Serum Samples

A serum sample should be collected from the donor and cryopreserved for retrospective testing when new tests are adopted for donor screening.

3.8 Semen Processed Prior to March 14, 2000

For semen processed prior to March 14, 2000, only the measures set out in Clause 6 apply.

4. REPEAT SCREENING & QUARANTINE

4.1 Repeat Screening

4.1.1 Serological Testing

The minimum serological tests outlined in Clause 3.5.2 should be repeated on new specimens obtained from the donor at least every 180 days while the donor remains an active participant in the program, and after interruptions exceeding 180 days.

4.1.2 Cytomegalovirus (CMV) IgM & IgG.

(a) Donors who tested positive for CMV IgG at the "Work-up" stage need not be retested for CMV IgG.

Note: If other tests show the presence of active infection in a CMV IgG positive donor, the donor should be deferred until the infection is resolved.

(b) Donors who tested negative for CMV IgG or CMV IgM at the "Work-up" stage should be retested every 180 days to detect seroconversion in the donor.

Note: Seroconversion from a negative to positive IgG or IgM status on retest implies an infection occurred shortly before the donor was recruited or during the testing interval, and semen donated during this period should be discarded.

4.1.3 Microbiological Testing

Repeat microbiological testing shall be performed at the time of each donation, as specified in Clause 5.

4.1.4 Physical Examination

A physical examination of the donor should be conducted at least every 365 days while the donor remains an active participant in the program, and after interruptions exceeding 365 days.

4.2 Quarantine and Repeat Screening

4.2.1 Quarantine Period

Fresh semen shall not be used for donor insemination. All donated semen must be frozen and quarantined for a minimum of 180 days.

Note: The quarantine period is to allow for the detection of seroconversion in the donor.

4.2.2 Repeat Screening Prior to Distribution

After the semen donation has been quarantined for a minimum of 180 days but before it is distributed,

(a) The donor must be re-evaluated on the basis of the exclusion criteria and still found not to be within a group set out under the heading "Exclusions" in Clause 2;

(b) The minimum serological testing set out in Clause 3.5.2, with the exception of 3.5.2(c), must be repeated on a new specimen obtained from the donor; and

(c) Serological testing for CMV IgG and CMV IgM should be repeated where the donor tested CMV IgG or CMV IgM negative at the "Work-up" stage, using a new specimen obtained from the donor.

4.3 Evaluation of Semen Safety

4.3.1 Role of the Medical Director or Physician Designated by the Medical Director

The Medical Director, who is responsible for the overall medical care, or his or her Physician Designate, shall determine and document whether semen may be released for distribution following a review of:

(a) Screening based on the exclusion criteria set out under the heading "Exclusions" in Clause 2;

(b) Donor infectious disease screening by serological and microbiological testing performed during the "Work-up" stage, as required under Clauses 3.5.2 and 3.5.4;

(c) Donor infectious disease screening by serological testing performed during the repeat testing, as required under Clause 4.2; and

(d) Microbiological testing performed as set out in Clauses 5.1 and 5.2.

4.3.2 Semen Release

Evaluation of the safety of the tested semen shall be confirmed prior to the semen being released for distribution.

4.4 Semen Processed Prior to March 14, 2000

For semen processed prior to March 14, 2000, only the measures set out in Clause 6 apply.

5. MICROBIOLOGY

5.1 *Chlamydia trachomatis and Neisseria gonorrhoeae*

A specimen collected from the donor at the time of each donation shall be tested for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* as specified in Clauses 3.5.4 (a) and (b).

5.2 General Culture and Sensitivity Evaluation

Semen cultures for each donation shall include a general culture and sensitivity evaluation.

Note: A positive test consists of any organisms not considered normal flora.

5.3 Antibiotics

If antibiotics are included in the cryoprotectant medium formulation, it should be documented because of possible antibiotic sensitivity or allergy in recipients.

5.4 Semen Processed Prior to March 14, 2000

For semen processed prior to March 14, 2000, only the measures set out in Clause 6 apply.

6. SEMEN PROCESSED PRIOR TO MARCH 14, 2000

6.1 Exclusion Criteria

(a) For semen fully processed prior to March 14, 2000, the criteria set out under the heading "Exclusions" of the CFAS 1996 Guidelines or those set out in Clause 2.1 of this Directive must have been applied.

(b) If, prior to March 14, 2000, semen has been collected but the repeat screening after a minimum quarantine period of 180 days has not been done, the repeat screening must be done in accordance with the criteria set out under Clause 2.1.

6.2 Serological Testing

6.2.1 Work-Up

For semen processed prior to March 14, 2000, the following minimum serological tests must have been performed at the "Work-up" stage:

(a) Antibody to HIV-1 and 2;
(b) Antibody to HCV;
(c) Hepatitis B surface antigen (HBsAg);
(d) Antibody to HTLV I and II; and
(e) *Treponema pallidum* (syphilis) using
    i. non-treponemal test; or
    ii. treponemal-specific test (FTA-ABS or MHA-TP).

6.2.2 Repeat Screening and Quarantine

6.2.2.1 Fully Processed Semen

For semen fully processed prior to March 14, 2000, the following tests must have been performed:

(a) Minimum serological testing performed at least every 180 days while the donor remained an active participant in the program must have included tests for:

    i. Hepatitis B surface antigen (HBsAg), unless the test for antibody to Hepatitis B core antigen (IgG anti-HBcAg) was done after a minimum quarantine period of 180 days; and
    ii. *Treponema pallidum* (syphilis) using a non-treponemal test or a treponemal-specific test (FTA-ABS or MHA-TP), unless both the non-treponemal test and

the treponemal-specific tests were done after a minimum quarantine period of 180 days; and

(b) Minimum serological testing performed after the semen was quarantined for a minimum of 180 days but before distribution must have included tests for:

i. antibody to HIV-1 and 2;
ii. antibody to HCV;
iii. hepatitis B surface antigen (HBsAg) or antibody to Hepatitis B core antigen (IgG anti-HBcAg);
iv. antibody to HTLV I and II; and
v. *Treponema pallidum* (syphilis) using:
A. non-treponemal test; or
B. treponemal-specific test (FTA-ABS or MHA-TP).

6.2.2.2 Partially Processed Semen

If, prior to March 14, 2000, semen has been processed but the repeat testing after a minimum quarantine period of 180 days has not been done, the repeat testing must be done in accordance with the requirements set out under Clause 4.2.2.

6.3 Microbiology

(a) For semen processed prior to March 14, 2000, the following minimum microbiological tests must have been performed at the "Work-up" stage and at least every 180 days while the donor remained an active participant in the program:

i. *Chlamydia trachomatis* using a nucleic acid amplification test on urine or urethral specimens; and

ii. *Neisseria gonorrhoeae* using
A. urethral or semen cultures; or
B. a nucleic acid amplification test on urine or urethral specimens.

(b) For semen processed prior to March 14, 2000 in respect of which the testing for *Chlamydia trachomatis* specified in clause 6.3(a)(i) has not been done, a nucleic acid amplification test for *Chlamydia trachomatis* must be performed:

i. on a semen specimen from the same donation as the semen that is to be distributed; or

ii on semen specimens from two donations made within 180 days of each other by the donor of the semen that is to be distributed, one of which was made before the donation of the semen that is to be distributed and one of which was made after that donation.

(c) For semen processed prior to March 14, 2000 in respect of which the testing for *Neisseria gonorrhoeae* specified in clause 6.3(a)(ii) has not been done, a nucleic acid amplification test for *Neisseria gonorrhoeae* must be performed:

i. on a semen specimen from the same donation as the semen that is to be distributed; or

ii on semen specimens from two donations made within 180 days of each other by the donor of the semen that is to be distributed, one of which was made before the donation of the semen that is to be distributed and one of which was made after that donation.

Note: Semen shall not be released for distribution if cultures rather than nucleic acid amplification tests were used for the detection of *Chlamydia trachomatis.*

(d) For semen processed prior to March 14, 2000, specimens collected between testing intervals in which *Chlamydia trachomatis* or *Neisseria gonorrhoeae* infection cannot be ruled out must be discarded.

6.4 Other Measures

In respect of matters other than testing for infectious diseases, semen processed prior to March 14, 2000 must have been processed in accordance with either:

(a) The measures set out under the headings "Work-Up", "Repeat Screening & Quarantine" and "Semen Microbiology" of the CFAS 1996 Guidelines; or

(b) The measures set out under the headings "Work-Up", "Repeat Screening & Quarantine" and "Microbiology" of this Directive.

7. ADDITIONAL INFORMATION

Questions concerning this Directive should be directed in writing to:

Blood and Tissues Division
Bureau of Biologics and Radiopharmaceuticals
3rd Floor LCDC Building #6
Postal Locator 0603C3, Tunney's Pasture
Ottawa, Ontario KIA 0L2

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Attention: Francisca Agbanyo, PhD