Supplementary Guidance Document for the Notification and Testing of New Substances: Organisms Used in Cell and Gene Therapy under Schedule 1 of the *New Substances Notification Regulations (Organisms)*

Health Canada

Environment and Climate Change Canada

December 2021

Supplementary Guidance Document for the Notification and Testing of New Substances: Organisms Used in Cell and Gene Therapy under Schedule 1 of the *New Substances Notification Regulations (Organisms)*

Purpose: This supplementary guidance document is intended to complement the *Guidelines for the Notification and Testing of New Substances: Organisms* (the Guidelines) and provides specific guidance to notifiers on addressing information requirements under Schedule 1 (for release Anywhere in Canada, which includes clinical trials) of the *New Substances Notification Regulations (Organisms)* [the Regulations] for substances that are animate products of biotechnology used in cell and gene therapy and administered to human patients. For more information on the New Substances Notification (NSN) process and post-notification regulatory obligations, please refer to Sections 9 and 10 of the Guidelines.

This document provides guidance only. It does not in any way supersede or modify the *Canadian Environmental Protection Act, 1999* (the Act) or the Regulations. In the event of an inconsistency between this document and the Act and/or the Regulations, the Act and the Regulations prevail.

1. GENERAL GUIDANCE

1.1 Regulatory Obligations under the Canadian Environmental Protection Act, 1999 and the Food and Drugs Act

The obligations to notify under the Act are independent of any obligations the notifier may have under the *Food and Drugs Act*. The information required under the Regulations must be provided to the New Substances (NS) program for the assessment of risks to the environment and human health under the Act.

The NS program now have access to Clinical Trial Applications (CTA) or New Drug Submissions (NDS) submitted to the Biologic and Radiopharmaceutical Drugs Directorate of Health Canada. If there is overlap between the information and data provided in a CTA and the information and data required in an NSN, the notifier can simply refer to the CTA in the relevant section of the NSN. When CTA is cited, it is necessary to refer the appropriate sections and page numbers of the CTA documents.
For general information regarding the regulatory obligations under the *Food and Drugs Act*and *Food and Drug Regulations*, please contact Health Canada's Biologic and Radiopharmaceutical Drugs Directorate (hc.brdd.dgo.enquiries.sc@canada.ca or 613-863-8405).

1.2 New Substances Notification Format

In an NSN, it is recommended that information requirements be addressed in a question and answer format by clearly indicating the information requirement being addressed, followed by the response. Information requirements should not be addressed by simply referencing a paper or by an unsupported statement. Rather, a written response should be supported with a cited paper, literature search, or data as appropriate. Example statements may be provided for certain information requirements, as described in the table below (see explanation under Section 1.3. General Statement, below). All supporting material should be provided in the NSN.

1.3 General statement

Where applicable, there is the option of copying the general statement (provided in italics in Section 2 Technical Requirements below) into the NSN form to respond to the information requirement. In such cases, results from a literature search and/or waiver requests are not necessary.

For information requirements which must be met with the submission of test data, a general statement will not be sufficient and a waiver request is required (see the Guidelines for more information on how to submit a waiver request).

1.4 Sections of Interest in the Guidelines

The following sections of the Guidelines contain relevant information to the notification of substances used in cell and gene therapies:

- Surrogate Organism (Sections 4.1; 4.2.7.1 and 7.3.2)
- Literature Search (Section 4.1)
- Waiver Request (Section 5)
- Pre-Notification Consultation (PNC) (Section 6): It is highly recommended that a PNC meeting be requested by contacting the NS Program (eccc.substances.eccc@canada.ca).
- Early Termination of the Assessment Period (Section 9.2.5): The NS Program will make every effort to align the assessment period for cell and gene therapy substances used in a clinical trial to match the CTA's 30-day assessment period, i.e. shortening the assessment period from 120 days to 30 days.

2. TECHNICAL INFORMATION REQUIREMENTS

This section explains the technical information requirements for micro-organisms which are human cell-based substances, non-replicating substances and replicating substances used in cell and gene therapy. Guidance related to each will be presented in individual chapters.

2.1 Substance Classification

2.1.1. Human Cell-based Substances (modified or non-modified)

Human cell-based substances include substances used in cell therapy which are:

- cultured non-modified human cells, or
- genetically modified human cells that carry a non-replicative/replication incompetent vector or carry no vector at all. For genetically modified human cells that contain a replicative vector, please refer to 2.1.3 (Replicating Substances).

Note: a separate notification is not requested for each patient treated with the cell therapy (e.g. for individualized therapies such as autologous CAR-T treatments). Instead, the cell type, its origin and genetic modification ("the platform") defines the substance that is notified by an importer or manufacturer.

2.1.2. Non-replicating Substances

Non-replicating substances include substances used in cell and gene therapy that are genetically modified to be incapable of replication except under specifically controlled conditions, such as non-replicative virus, non-replicative bacterium or non-replicative vector.

Where sufficient evidence cannot be provided to support the claim that the substance is a non-replicative/replication incompetent, then the substance is considered to be a replicating substance.

2.1.3. Replicating Substances

Replicating substances include substances used in gene therapy that have the capacity to divide or replicate in the human body and/or in the environment such as a replicative vector (including a human cell-based substance that contains a replicative vector), oncolytic virus or oncolytic bacterium.

2.2 Shedding

If available, provide shedding data for the notified substance. When the notifier claims that the notified substance cannot be shed into the environment, shedding data from animal studies and/or human studies using the notified substance and/or a suitable surrogate substance, or any other data or information must be provided to support the claim.

2.3 Explicit biological name for substances used in cell and gene therapies:

The explicit biological name is used to uniquely describe a living organism for the purposes of publication in the *Canada Gazette* (refer to Appendix 4 of the NSNR (Organisms) guidelines for general advice on proposing an explicit biological name for organisms). To uniquely describe a living organism used in cell and gene therapies, the following features of the living organism should be included in the proposed explicit biological name:

- type of substance, with taxonomic strain designation of bacteria or serotype for viruses (e.g., human T cells; *Listeria monocytogenes* strain 123; or chimpanzee derived adeno virus serotype 5, etc.);
- recombinant or wild type;
- replicative or non-replicative;
- name(s) and source(s) of inserted or deleted gene(s) contributing to the therapeutic action(s) due to the genetic modifications;
- unique code (e.g., ABCD12). This could be a trade name, company code name or other relevant code name.

Examples of explicit biological names:

- Recombinant Human T-cell with a disrupted *X* gene (ABCD12);
- Recombinant and non-replicative chimpanzee derived adeno virus serotype 5 encoding *X* gene (ABCD12);
- Recombinant human adenovirus-serotype 2 with tumour-specific replication and expressing multiple human immunomodulatory genes (ABCD12);
- Recombinant Human T-cell transduced with a replicative lentiviral vector serotype 2 expressing a chimeric antigen receptor binding the human B-cell CD19 antigen (ABCD12).

SCHEDULE 1 – INTRODUCTION ANYWHERE IN CANADA - NOTIFICATION INFORMATION REQUIREMENTS

Guidance for human cell-based substances (modified or non-modified)

1. The following information in respect of the micro-organism:

1(a) its identification and the information substantiating its identification

[Note: This information is also required in a CTA or NDS]

The notified substance should be assigned a valid and well-supported taxonomic designation. That taxonomic designation will serve as the cornerstone of the notification and the risk assessment.

The notifier should make a reasonable effort to establish and validate the designation that will be used to identify the substance.

Describe the type of cell (for example, CD8 T-cell, CD4 T-cell, NK cell, monocyte), its origin (for example, blood, organ, tumor) and how it was harvested, if applicable.

Where the substance has been genetically modified, the identity of the substance should include sources of genetic material and modifications.

For cells modified using a vector, provide a FASTA format file of the genome of the vector.

For cells modified using a vector, provide a well-documented rationale supporting the claim that the vector will not replicate outside the human body.

1(b) its common and superseded names and any synonyms

[Note: This information is also required in a CTA or NDS]

Provide any common and superseded names for the notified and parental substance/strain as well as its synonyms. All known internal company codes, culture collection designations and synonyms referenced in test study reports or literature should also be provided.

If there are none, then this should be specified.

1(c) its strain history

[Note: This information is also required in a CTA or NDS]

Provide information on the history of the notified substance from its original isolation (from human autologous or allogeneic donors) until its final development as the notified substance. This information should include:

1. Information and/or copies of any published reports pertaining to the isolation of the human cells.
2. A detailed description of the notified substance's development from the parental and ancestral lineages to its current form including the construction of any vector used to carry genetic material to the cell, and the substance's chain of custody. If available, this should include:
    i. The names of intermediate cells and a description of novel traits;
    ii. The origin of the synthetic DNA used, if applicable;
    iii. Details of previous genetic modifications and/or selection practices, a description of how the modifications were made, the location of these changes (chromosome(s), gene(s) or plasmid(s), and if any introduced DNA is found within a transposable element) and any GenBank records, other than those modifications already described in the section addressing the description of any modifications to the substance (paragraph 1(d) of Schedule 1); and
    iv. All storage and culturing conditions (including the type of media used for growing the substance and the final viral vector used to transduce it).
3. If the notified substance was deposited into one or more culture collection banks, the name of the repository(s) and accession number(s) used (e.g., American Type Culture Collection ATCC 1234).

1(d) a description of any modifications to the micro-organism, including:

1(d)(i) the purpose of the modifications

[Note: This information is also required in a CTA or NDS]

Provide a description of the purpose of each modification made to the substance. If the substance has not been modified, then this should be specified.

1(d)(ii) the methods and steps taken to make the modifications

[Note: This information is also required in a CTA or NDS]

Describe the methods and steps taken to make directed or deliberate modifications to the substance. If the substance has been modified using recombinant DNA or genome editing techniques, the description should include the following:

- cloning strategies and procedures including clearly labeled schematic representations of the modifications made;
- vector construction details (e.g., viruses in gene therapy used to modify cells), and information on the functional elements within the vector and reason(s) for their removal or retention (promoters and other regulatory elements, replication elements, structural genes, selective markers, etc.);
- vector characteristics (shuttle, conjugative, self-transmissible, mobilizable);
- DNA transfer methods employed (conjugation, transformation, transduction, electroporation, microinjection, ballistic injection); and
- the inserted and/or modified sequences or the expression cassette, and in the case of insertions, the copy number of the inserts and/or the copy number of vectors; in the case of deletions, the size of the deleted regions as well as its functional characteristics.

1(d)(iii) the phenotypic and genotypic changes that resulted from the steps referred to in subparagraph 1(d)(ii)

[Note: This information is also required in a CTA or NDS]

Describe changes in physiological characteristics and biological functions known to have resulted from the modifications to the substance. This should also include unintended changes.

The description of genetic changes could be based on:

- restriction enzyme analysis
- restriction map
- nucleic acid hybridization (gene probe) analysis (e.g., Southern Blot analysis)
- PCR
- DNA sequence analysis
- electrophoretic analysis

The description of phenotypic changes should be based on one or more of the following:

- expression of products of inserted genetic material (e.g., Western blot analysis, HPLC, RT-PCR, etc.)
- response in relation to the inserted selection markers, if applicable

- physiological changes based on inserted, modified or deleted genetic material
- flow cytometry data

Provide full copies of all referenced test reports and/or assays.

1(d)(iv) the stability of the changes referred to in subparagraph 1(d)(iii)
[Note: This information is also required in a CTA or NDS]

Describe the stability of the phenotypic and genotypic changes known to have resulted from the modifications to the substance.

The information provided in paragraph 2(f) (shelf life test data) and sub-paragraph 1(d)iii (phenotypic and genotypic changes**)** of Schedule 1 may be referenced.

When using a non-replicating vector, provide information on the screening for absence of replication-competent vector, if applicable.

Provide full copies of all referenced test reports.

1(d)(v) the nature, source and function of any inserted genetic material
[Note: This information is also required in a CTA or NDS]

Describe the nature, source, and function of any genetic material introduced into the substance following modification, by any means, including the:

- size of the introduced genetic material;
- source of any inserted genetic material, including the taxonomic designation of donors;
- functional characteristics of inserted genetic material (for example, regulatory function, origin(s) of replication, coding or non-coding sequences, selection markers, promoter);
- the nucleotide sequence (in FASTA format) or its accession number in a public database and a sequence analysis; and
- copy number and location of inserted genetic material, if applicable.

If no genetic material is inserted, then this should be specified.

1(e) a description of the methods that can be used to distinguish and detect the micro-organism
[Note: This information is also required in a CTA or NDS]

Describe available methods that could be used to detect the substance (for example: in a product or in the environment) and distinguish it from background levels. Information provided in subparagraph 1(d)(iii) of Schedule 1 may be referenced. If no methods exist or none have been developed, a method should be proposed. Methods described or proposed should be supported by scientific evidence as to their validity.

1(f) a description of the biological and ecological characteristics of the micro-organism, including:

1(f)(i) its life cycle
The following statement may be included to meet the information requirement if it is applicable:

The notified substance is a human cell. As mentioned in subparagraph 1(f)(v), human cells require specific conditions to survive, grow and replicate which are not found outside the human body. A description of the life cycle outside of the human body is not available as it will not survive or replicate outside the human body.

1(f)(ii) its infectivity, pathogenicity to non-human species, toxicity, and toxigenicity
The following statement may be included to meet the information requirement if it is applicable:

The notified substance is a human cell. Human cells are not known to infect, be pathogenic, toxigenic or toxic to non-human species.

1(f)(iii) its resistance to antibiotics and tolerance to metals and pesticides
Antimicrobial susceptibility (including antibiotic resistance) is addressed in paragraph 6(b) of Schedule 1.

The following statement may be included to meet the information requirement if it is applicable:

The notified substance is intended solely for introduction into the human body, therefore tolerance to metals and pesticides in the environment is not expected.

1(f)(iv) its involvement in biogeochemical cycling
The following statement may be included to meet the information requirement if it is applicable:

The notified substance will have no direct role in the biogeochemical cycling process.

1(f)(v) the conditions required for, and conditions that limit, its survival, growth and replication
[Note: This information is also required in a CTA or NDS]

The following statement may be included to meet the information requirement if it is applicable:

The notified substance is a human cell and human cells require specific conditions (sterility, temperature, nutrient, pH) to survive, grow and replicate which cannot be found outside the host (with the exception of specific conditions artificially recreated in laboratory settings).

1(f)(vi) the mechanisms of its dispersal and the modes of interaction with any dispersal agents
The following statement may be included to meet the information requirement if it is applicable:

The notified substance is a human cell. As mentioned in subparagraph 1(f)(v), human cells require specific conditions to survive, grow and replicate which are not found outside the human body. As it will not survive or replicate outside the human body, human cells will not disperse outside the human body.

1(g) a description of the mode of action in relation to the intended use
[Note: This information is also required in a CTA or NDS]

Describe the mode of action of the substance in relation to its intended use. The mode of action means the underlying mechanisms through which the substance performs its function (e.g., antigen expression which will induce production of antibodies).

Information collected during product development and efficacy studies, as well as information from a literature search, may fulfill this information requirement. Include pre-clinical and/or clinical trial test data, if available. Provide detailed summaries from the Investigator's Brochure and/or full copies of referenced test reports. A flow diagram may be provided to illustrate the mode of action, if available.

1(h) the identification of any patent or any application for a patent, as the case may be

In the event that the notifier has been granted or have applied for a patent specific to the notified substance or the final product containing the notified substance, in Canada or elsewhere, the following information should be provided:

1. The authority under which the patent was issued or applied for;
2. The patent number or application number; and
3. A copy of the patent, or the patent application, or a web link to the patent.

If no patent has been granted or applied for, this should be indicated.

1(i) the dispersal by gene transfer of traits of pathogenicity to non-human species, toxigenicity and resistance to antibiotics, including a description of:

1(i)(i) the genetic basis for pathogenicity to non-human species, toxigenicity and resistance to antibiotic

Antimicrobial resistance (including antibiotic resistance) is addressed in paragraph 6(b) of Schedule 1.

The following statement may be included to meet the information requirement if it is applicable:

The notified substance is a human cell and there is no genetic basis for pathogenicity or toxigenicity to non-human species. As mentioned in subparagraph 1(f)(ii), human cells are not known to infect, be pathogenic, toxigenic or toxic to non-human species.

1(i)(ii) the capability to transfer genes

The following statement may be included to meet the information requirement if it is applicable:

The notified substance is a human cell. As mentioned in subparagraph 1(f)(v), human cells require specific conditions to survive, grow and replicate, which are not found outside the human body. As it will not survive or replicate outside the human body, there will be no opportunity to transfer genes.

1(i)(iii) the conditions that might select for dispersal of traits of pathogenicity to non-human species, toxigenicity and resistance to antibiotics, and whether the conditions are likely to exist at the locations of introduction or within the range of dispersal of the micro-organism

The following statement may be included to meet the information requirement if it is applicable:

There are no known conditions that might exist at the location of introduction or within the range of dispersal that might select for dispersal of traits of pathogenicity to non-human species, toxigenicity or antimicrobial resistance.

1(j) a description of the geographic distribution of the micro-organism

The following statement may be included to meet the information requirement if it is applicable:

The notified substance's geographic distribution is determined by the locations of manufacturing facilities, treatment sites and the humans/hosts/recipients receiving the biologic drug containing the notified substance.

2. The following information in respect of the manufacture and importation of the micro-organism:

2(a) the identification of trade names and manufacturers, importers and vendors

[Note: This information is also required in a CTA or NDS]

Indicate all known or foreseen trade names for the substance, including names previously used to identify the substance or its formulation.

Also indicate the name of the manufacturer of the substance, and if the substance is to be imported into Canada, the names of the importers, and the complete listing of names and addresses of all potential and/or confirmed distribution points (for example, vendors, clinical trial sites, formulators/blenders). If there are no trade names, manufacturers, importers or vendors, then this should be specified.

Provide information related to the clinical trial site(s) and the parameters used to select the location of the clinical trial site(s). If a clinical trial site has not yet been selected, parameters used to select the location of the clinical site will be sufficient to address the information requirement.

2(b) the identification of locations of manufacture in Canada

[Note: This information is also required in a CTA or NDS]

Identify all intended locations (address) of manufacture of the substance in Canada. If there are no manufacturing locations in Canada, this should be specified.

2(c) the physical state of the formulation

[Note: This information is also required in a CTA or NDS]

Describe the physical form of the substance in the formulation (for example, powder, solution or mist).

2(d) the concentration of the micro-organism in the formulation

[Note: This information is also required in a CTA or NDS]

Provide the concentration of the substance in the commercial formulation. Examples of units for concentration that may be used include, but are not limited to:

- colony forming unit per millilitre (CFU/mL) or per gram (CFU/g)
- number of spores per millilitre (Spore/mL) or per gram (Spore/g)
- plaque forming unit per millilitre (PFU/mL) or per gram (PFU/g)
- viral particle per millilitre (VP/mL) or per gram (VP/g)
- fluorescent focus unit per millilitre (FFU/mL) or per gram (FFU/g)
- tissue culture infectious dose (TCID)
- genome copy per millilitre (GC/mL) or per gram (GC/g)
- number of cells per millilitre (cells/mL) or per gram (cells/g)

2(e) the identification and concentration of other ingredients and of any contaminants in the formulation

[Note: This information is also required in a CTA or NDS]

Provide a list of all the components (both active and inactive ingredients) that make up the formulation, including the relative concentration of each ingredient. For example, any substance that is added to the formulation in order to stimulate growth or metabolic activity of the notified substance and any carrier medium should be identified. A certificate of analysis based on representative samples should also be provided.

2(f) the viability of the micro-organism in the formulation

[Note: This information is also required in a CTA or NDS]

Provide the viability and expected shelf life of the substance in the formulation, taking into consideration the recommended storage procedures. Express shelf life as the percentage of viable cells remaining in the formulation after a specific storage period, calculated from the viability at the time of production and the viability at the end of the projected shelf-life. Provide full test reports referenced. If test data is not yet available, then this should be specified.

2(g) a description of any recommended storage and disposal procedures

[Note: This information is also required in a CTA or NDS]

Information on storage procedures should include:

- a description of any recommended storage conditions (e.g., lighting, humidity, temperature, etc.);
- type of containers used to store or transport the substance formulation (e.g., vial, bucket, tote, leak-proof, puncture-resistant, impact resistant, fitted with lids); and
- any recommendations for storage of the end-use product.

Information on disposal procedures should include:

- A description of any recommended disposal procedures of unused portions of substance and its formulation, including those recommended to the end-user, if applicable.

If there are no recommended storage and disposal procedures or if such procedures are not necessary, then this should be specified.

2(h) an estimation of the quantity of the micro-organism that will be imported into or manufactured in Canada, as the case may be

[Note: This information is also required in a CTA or NDS]

Provide an estimate of the quantity of substance to be manufactured or imported, including the quantity manufactured or imported during the first 12 months, and the expected maximum quantity manufactured or imported in any 12-month period during the first three years.

Quantitative units (volume, mass or quantity of the substance) should reflect the physical state of the formulation (for example, CFU, mL for liquids, or g for solids).

The predicted or known number of doses and the concentration of the therapeutic agent in the doses for one treatment (for example, one treatment consists of 4 doses of 10^8 pfus/mL), or the infectious unit per dose of the vaccine, to be imported or manufactured should also be provided. This can be related to the estimated number of participants in the trial, if known.

2(i) a description of the equipment and methods of manufacture and of quality control and quality assurance procedures

[Note: This information is also required in a CTA or NDS]

Describe:

- the equipment used;
- the manufacturing process (e.g., open/closed loop operations);
- the nature of the production process (i.e., batch or continuous);
- scale of the process;
- maintenance of the cell bank;
- culture methods and conditions (e.g., submerged fermentation, media composition, temperature, etc.);
- any containment measures and emergency contingency plans in place;
- waste treatment; and
- long-term storage options (e.g., storage in liquid nitrogen, lyophilisation, etc.).

The description should also include floor plans that indicate the flow of personnel, material and product, and a flow diagram of the manufacturing process identifying the points of entry or exit of all raw materials and waste materials.

Also describe any quality control and assurance procedures used to manufacture the substance such as:

- monitoring results;
- verification of strain integrity (phenotypic and genotypic identity);
- certificate of analysis of the product containing the substance;
- description of batch testing (number, frequency, range and tolerance limits); and
- measurement of contaminants, residues and impurities.

If the substance is imported and not manufactured in Canada, a summary of the method of manufacture including formulation preparation and QA/QC procedures should be provided.

2(j) a description of the location of manufacturing facilities in Canada

[Note: This information is also required in a CTA or NDS]

Describe each manufacturing location in Canada, including the surrounding area and the proximity of each manufacturing location to populated areas, agricultural areas and watercourses.

This description should adequately describe any containment measures in place at the facility and could include the following:

- the layout of the facility (e.g., diagram or schematic);
- a list of personnel and their training;
- a list of material and product flow in the facility;
- a description of containment features (e.g., exhaust filters, closed loop cycling, etc.);
- a description of standard operating procedures which are followed to ensure containment of the substance;
- a description of security measures in place at the facility;
- a description of procedures in place to report accidents at the facility;
- a description of any culture transfers between unit operations;
- a description of procedures for inactivating the substance;
- a description of procedures for the storage and disposal of unused portions of the substance; and
- a description of emergency response measures for handling small and large spills involving the substance.

If there are no locations of manufacture in Canada, then this should be specified.

2(k) a description of the nature of potential releases of the micro-organism from the manufacturing facilities in Canada or from facilities to which the micro-organism will be imported, as the case may be, and the procedures to control releases
[Note: This information is also required in a CTA or NDS]

Describe any intended or potential emissions or releases of the substance, including treated and untreated releases (liquid, solid, gaseous), from the manufacturing facility or the facility to which the substance will be imported, including clinical trial sites.

Estimate the amount of substance and/or metabolites of concern expected to be released in effluents and emissions during batch or continuous operations. The description should include the number of batches to be produced in a year and the volume of the effluent.

Provide a description of any standard operating procedures in place to limit releases from the facility, including any territorial, provincial or municipal regulations or by-laws adhered to, to prevent widespread release.

2(l) a description of the procedures for the treatment and disposal of wastes containing the micro-organism from the manufacturing facilities in Canada
[Note: This information is also required in a CTA or NDS]

Describe the management of wastes from manufacturing facilities. These may be part of quality control and quality assurance procedures already in place at the manufacturing facility. The handling and disposal of waste includes but is not limited to solid wastes (e.g., biomass, gloves, single-use contaminated materials, re-usable contaminated materials, etc.), liquid wastes (e.g., effluents, spent media, samples, etc.) and gaseous exhausts or other emissions. Provide copies of procedures used.

Containers used for the storage or transport of waste before disposal should be described (e.g., volume, sealed, leak-proof, labelled, etc.). When waste disposal is outsourced, this should be specified, and information regarding the methods used by the company and location of disposal should be provided. Appropriate municipal and/or provincial regulations regarding disposal should be referenced and followed.

Provide kill rates or other evidence of the efficacy of the treatment methods (physical or chemical) used when describing the treatment procedures for solid, liquid and gaseous wastes. Results may be provided as a certification of analysis, in-house data or information from the literature, and should demonstrate a reduction in the viability or a decrease in the number or concentration of cells, spores, viral particles, etc. This can be expressed as a percentage of reduction in viability of substance for a given method/timeframe or another well-described and relevant unit of measure to demonstrate that the treatment method described is effective.

When municipal, provincial or federal statutes, regulations or by-laws are referenced, provide a copy of the relevant portion. Also provide copies of permits, licences, certificates or any other required approval regarding the discharge or disposal of waste from the manufacturing facility.

Where the notified substance produces secondary metabolites (including toxins) that may be secreted into liquid media or present in wastes, the efficacy of inactivation or containment of those metabolites should be described when discussing the treatment methods and waste disposal procedures.

If there are no procedures in place for the treatment and disposal of wastes or if such procedures are not necessary, then this should be specified.

In the case of import only, provide information on the disposal of contaminated materials and wastes to meet the requirements in paragraphs 3(e) and 3(f) of Schedule 1.

3. The following information in respect of the introduction of the micro-organism:

3(a) the intended and potential uses

[Note: This information is also required in a CTA or NDS]

Describe the substance's intended use, linked to the known mode of action. Information from the clinical trials and from the Investigator's Brochure may be provided, or links to previous sections in the NSN describing the clinical trials may be referenced.

Potential uses may include plans for clinical trials for treatment of other diseases or commercialization of product(s) containing the notified substance.

3(b) the history of use

[Note: This information is also required in a CTA or NDS]

Describe the history of use of the substance in Canada or any other country. Information from previous or on-going clinical trials and/or the Investigator's Brochure may support this information requirement.

3(c) a comparison of the natural habitat of the micro-organism to the habitat at potential locations of its introduction, and the nature of the selection that may operate on the micro-organism at the potential locations of introduction

The following statement may be included to meet the information requirement if it is applicable:

The notified substance is introduced into the human body, which is considered to be the natural habitat of the substance.

3(d) a description of procedures for the introduction of the micro-organism, including:

3(d)(i) the method of application

[Note: This information is also required in a CTA or NDS]

Describe the proposed equipment for and methods of application of the substance, including how the substance will be administered to patients.

This should also include:

- the physical form of the substance;
- the nature of the formulation; and
- the method of administration of the formulation.

Also describe any necessary biosafety procedures such as handling precautions and personal protective equipment.

3(d)(ii) the quantity, frequency and duration of application

[Note: This information is also required in a CTA or NDS]

Describe the intended and recommended quantity (number of doses and dose concentration), frequency, and duration of application for the substance.

Provide details of the clinical trial and Investigator's Brochure. For an approved therapeutic product, also provide the treatment dosage and the frequency of the duration of a typical treatment.

3(d)(iii) any activities associated with the introduction

[Note: This information is also required in a CTA or NDS]

Administration of other therapeutic products in relation to the clinical trial or monitoring of patients should be specified, if applicable. A copy of the Product Monograph or any instructions given to the patients may also be provided, if available. If there aren't any other activities associated with the introduction of the substance, then this should be specified.

3(e) a description of any contingency plans in the event of an accidental release

Describe any contingency plans for handling accidental releases of the substance during its transport, storage, handling, use and disposal. These plans may include any available information on procedures

and equipment for decontamination, removal and control, as well as training and criteria for determining when contingency plans should be initiated.

If there are no contingency plans, then this should be specified.

3(f) a description of any recommended procedures for terminating the introduction of the micro-organism
[Note: This information is also required in a CTA or NDS]

Provide information concerning disposal of the unused portion of the substance. This includes information pertaining to the return of the substance or product to the supplier, manufacturer or pharmacy. Also provide any procedures in place or parameters for terminating the clinical trial, and procedures followed to treat and dispose of biohazardous wastes. Indicate whether regional or national regulations are being followed.

If there are no procedures for terminating the introduction of the substance, then this should be specified.

4. The following information in respect of the environmental fate of the micro-organism

4(a) the identification of the plant and animal species likely to be exposed and, if infectivity, pathogenicity to non-human species, toxicity and toxigenicity have been identified under subparagraph 1(f)(ii), the identification of the receptor species likely to be exposed
Either of the following statements may be included to meet the information requirement as applicable:

Given that there is no shedding or intended release of the notified substance to the environment, no plant or animal species are expected to be exposed.

Or

Given that there is shedding or potential release of the notified substance to the environment, any plant or animal species that a treated human comes into contact with in the Canadian environment may potentially be exposed.

4(b) a description of habitats where the micro-organism may persist or proliferate
The following statement may be included to meet the information requirement if it is applicable:

As mentioned in subparagraph 1(f)(v), the notified substance does not replicate or survive outside the human body, therefore it is not expected to persist or proliferate in the environment.

4(c) the estimated quantities of the micro-organism in the air, water and soil at the points of introduction, and the estimated population trends
The following statement may be included to meet the information requirement if it is applicable:

As mentioned in subparagraph 1(f)(v), the notified substance does not replicate or survive outside the human body, therefore it is not expected to persist or proliferate in the environment. Estimates in the environment are therefore not relevant.

4(d) any other information on the environmental fate of the micro-organism
Provide any other known information on the persistence, proliferation, dispersal or any other relevant characteristic to predict the fate of the substance in the environment.

If there is no additional information, then this must be stated or the NSN will be deemed incomplete.

5. The following information in respect of the ecological effects of the micro-organism:

5(a) the data from tests conducted to determine the effects of the micro-organism on:

5(a)(i) aquatic plant, invertebrate and vertebrate species likely to be exposed to it
Provide results from three tests detailing the substance's effects on key aquatic species. This includes tests for each of the following species:

- Aquatic plant species
- Aquatic vertebrate animal species
- Aquatic invertebrate animal species

If a waiver is requested under paragraph 106(8)(a) of the Act in respect of this regulatory requirement, the waiver request should:

- Indicate that a waiver is requested under paragraph 106(8)(a) of the Act to meet the data requirement of subparagraph 5(a)(i) of Schedule 1 of the Regulations.

Explain that human cells are not toxic to aquatic species, and that the notified substance does not replicate or survive outside the human body, therefore it is not expected to be introduced into the environment or have effects on aquatic species if introduced in the environment.

5(a)(ii) terrestrial plant, invertebrate and vertebrate species likely to be exposed to it
Provide results from three tests detailing the substance's effects on key terrestrial species. This includes tests for each of the following species:

- Terrestrial plant species
- Terrestrial vertebrate animal species
- Terrestrial invertebrate animal species

If a waiver is requested under paragraph 106(8)(a) of the Act in respect of this regulatory requirement, the waiver request should:

- Indicate that a waiver is requested under paragraph 106(8)(a) of the Act to meet the terrestrial plant, vertebrate and invertebrate data requirements of subparagraph 5(a)(ii) of Schedule 1 of the Regulations.

Explain that human cells are not toxic to terrestrial plant, vertebrate and invertebrate species, and the notified substance does not replicate or survive outside the human body, therefore it is not expected to be introduced into the environment or have effects on these species if introduced in the environment.

5(b) the involvement of the micro-organism in adverse ecological effects
The following statement may be included to meet the information requirement if it is applicable:

As mentioned in subparagraph 1(f)(v), the notified substance does not replicate or survive outside the human body, therefore it is not expected to be involved in:

- *any adverse effects related to plants and animals, microbiota, or ecological processes (including physico-chemical effects); and*
- *any other adverse ecological effect not already addressed under any other information requirement.*

5(c) the potential of the micro-organism to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity

The following statement may be included to meet the information requirement if it is applicable:

As mentioned in subparagraph 1(f)(v), the notified substance does not replicate or survive outside the human body; therefore it is not expected to have an adverse environmental impact that could affect the conservation and sustainable use of biological diversity.

6. The following information in respect of the human health effects of the micro-organism:

6(a) any documented involvement of the micro-organism in adverse human health effects and a description of the characteristics of the micro-organism that distinguish it from known pathogens

[Note: This information is also required in a CTA or NDS]

Provide information related to the involvement or the potential involvement of the notified substance in any adverse human health effects (e.g., infections, diseases, symptoms of diseases or conditions, toxic effects, allergic reactions, etc.).

This requirement may be fulfilled by providing a review of the scientific literature and detailing documented involvement or potential involvement of the notified substance and/or suitable surrogate substance in adverse human health effects, or lack thereof, as applicable.

The scientific literature review should indicate the literature search strategy used (keywords and time period) and databases used and should address the following:

- the number of cases reported or incidence in a population;
- demographics of the reported cases (e.g., elderly, children, immuno-compromised individuals, otherwise healthy, etc.);
- the nature and severity of the effects (e.g., superficial, systemic, deep infections, acute, chronic, symptoms, etc.);
- type of exposure leading to the adverse effects; and
- geographic locations where reported cases are prevalent.

Literature search terms to be used in combination with the parental or wild type strain name may include:

adverse effect*, disease*, hazard*, immuno*, allergen*, infect*, invasi*, outbreak, opportunistic, pathogen*, risk*, virul*, resist*, compromis*, chronic, acute, sick*, report*, case report*, hospital, clinical, death, human, health

If the substance or introduced genetic material is not associated with adverse human health effects, provide the scientific literature search strategy (keywords and time period) and databases used, showing that there are no relevant results.

Information and data from previous clinical trials may be provided to satisfy this data requirement. Information and test data described in the Investigator's Brochure may be cited and referenced.

After the end of the assessment period of the NSN:

If new adverse human health effects are reported following the use of the notified substance, then this information must be provided to the NS program as soon as possible after learning of it. The notified substance will be subject to a re-evaluation once the additional information is provided.

6(b) the data from tests of antibiotic susceptibility

If a waiver is requested under paragraph 106(8)(a) of the Act in respect of this regulatory requirement, the waiver request should:

- Indicate that a waiver is requested under paragraph 106(8)(a) of the Act to meet the data requirement of paragraph 6(b) of Schedule 1 of the Regulations.
- Confirm the absence of antimicrobial (antibiotic or antiviral or antifungal) resistance genes as described in paragraph 1(d) of Schedule 1.
- Include the following statement explaining why the test is not needed in order to determine whether the substance is toxic or capable of becoming toxic:

  Human cells are generally resistant to antimicrobial drugs.

6(c) the data from tests of pathogenicity that are valid for related micro-organisms that are pathogenic to humans

[Note: This information is also required in a CTA or NDS]

The data requirement refers to pathogenicity testing performed on the substance to determine its pathogenicity to humans, including infectivity, latency, clearance from tissues and organs, and potential toxicological effects.

Data from pre-clinical and clinical trials may be provided to satisfy this data requirement. Reference may be made to test data described in the Investigator's Brochure. Provide all information necessary for a complete and accurate description of the test procedures and results, and all test data (including supporting raw data) and analysis necessary for the NS program to reach an independent conclusion. Copies of signed certification documents should be provided when claiming any accreditation or certification (such as *Good Laboratory Practice* or *Clinical Laboratory Improvement Amendments*).

If a waiver is requested under paragraph 106(8)(a) of the Act in respect of this regulatory requirement, the waiver request should:

- Indicate that a waiver is requested under paragraph 106(8)(a) of the Act to meet the data requirement of paragraph 6(c) of Schedule 1 of the Regulations.

- Explain why the test is not needed in order to determine whether the substance is toxic or capable of becoming toxic.

6(d) the potential for adverse immunologic reactions in persons exposed to the micro-organism

[Note: This information is also required in a CTA or NDS]

Provide information on the ability of the notified substance to elicit adverse immune reactions (e.g., allergic reactions, delayed hypersensitivity, etc.).

Include details on:

- the type and severity of effect (expected or unexpected);
- the nature of exposure preceding the effect;
- the frequency, duration and severity of the effect;
- a brief description of the clinical methods available to manage the effects, if applicable; and
- the proportion of persons exposed who displayed the reaction.

If information available indicates that no adverse immune reactions are reported in persons exposed to the notified substance, the notifier should still indicate the duration of the potential exposure, the nature of this potential exposure, and the system in place for reporting effects.

Relevant information on immunologic reactions from all pre-clinical and clinical trials should also be provided.

6(e) the estimated number of persons who may become exposed and the degree of their exposure to the micro-organism

Provide an estimate of the number of persons (in occupational settings and in the general public) who may be exposed to the substance in Canada during:

- manufacturing in Canada (including research and development, pilot plant, and commercial production);
- transportation and handling;
- processing;
- storage;
- intended use (e.g., patients, trained nurses, clinicians, patient contacts); and
- disposal, destruction, and recycling.

Also provide:

- the number of clinical trials and the number of participants in each clinical trial (and if future clinical trials are planned, provide an estimated number of trials and an estimated number of participants in each trial);
- information on the incidence of the disease in Canada. For example: “It is estimated that the disease for which this treatment has been developed afflicts 10,000 people per year in Canada”; and
- an estimate of the number of patients who would be expected to receive the substance as part of their treatment should the substance be commercialized.

7. All other information and test data in respect of the micro-organism that permit the identification of hazards to the environment and human health and that are in the person's possession or to which the person may reasonably be expected to have access

"All other information" refers to any relevant information not already provided as part of a response to an information requirement. This information should include a summary of all other information and test data with respect to the substance that are in the possession of the person (i.e. manufacturer or importer) or to which they may reasonably be expected to have access.

"In the possession of the person (i.e., manufacturer or importer)" means the information in:

- the company's offices in Canada if the NSN was submitted by a Canadian company; and/or
- the foreign company's offices if the NSN was submitted by a foreign company through a Canadian Agent.

"To which they may reasonably be expected to have access" means information in any of the company's offices worldwide, or other locations where the notifier can access the information.

A summary of the additional information available should be provided giving sufficient detail regarding methodology and results to permit the NS program to determine the relevance and scientific validity of the information.

The NS program may request to see the available information or a full test report (in the case of test data, including raw data) after reviewing the summaries provided.

Any additional information provided should be relevant to identifying hazards to the environment and human health and relevant to the degree of environmental and human exposure to the substance. This may include, for example:

- Experimental data (including negative and positive results);
- Investigator's Brochure;
- Product Monograph, if available;
- Safety Data Sheet, if available;
- Results of scientific literature searches, including information sources (databases), time period searched, search strategy and terms used;
- Product incident reports or results of studies indicating the risk to employees, consumers, customers, public, or the environment (environmental assessment or environmental fate modelling) that may result from the use of the substance;
- Information and data demonstrating efficacy;
- Risk assessments previously conducted on the notified substance (for example, an environmental risk assessment conducted for another agency).

If there is no information or data other than the information already provided in the NSN, then this should be specified.

8. The identification of other government agencies, either outside or within Canada, that the person has notified of the manufacture or importation of the organism, and the purpose of that notification

Provide any known instance(s) when the manufacture or importation of the substance has been notified to other government agencies, either outside or within Canada, and the purpose of such notification(s).

Include:

1. if known, the identity of the government agency, including the complete name, city and country where the government agency is located; and
2. if known, the government agency's file number, the outcome of the assessment and if applicable, the risk management measures imposed by the agency.

For example:

- a CTA has been submitted to Health Canada; or
- an American supplier has notified the United States Environmental Protection Agency under the provisions of the *Toxic Substances Control Act* (TSCA).

If no other government agency has been notified, this should be specified.

9. A description or specification of the test procedures followed in developing the test data, including the test methods, reference substances and quality control and quality assurance procedures
[Note: This information is also required in a CTA or NDS]

When data is provided to address an information requirement, the test conditions, procedures and protocols used to develop and report the test data should be clearly described. Test conditions and procedures should be consistent with established standard methods.

Clearly indicate the test that was used and its source. Also provide a description of the test procedures, including but not limited to:

- identification of the test substance, including any identification or reference numbers used in the study report;
- description of negative and positive controls used and any other relevant strains used for comparison, if applicable;
- quality control and quality assurance procedures;
- a detailed description of the test procedure followed, referencing any standard tests and identifying any deviations from standard or planned protocols; if the test was conducted according to the practices set out in the "Principles of Good Laboratory Practice (GLP)", the required GLP and Quality Assurance statements and documentation; and
- if the test was conducted according to a specific standard other than GLP, the name and address of the test facility, name of the person responsible for the study and the person's signature, dates on which the study was initiated and completed, and if applicable, certification or accreditation documentation.

Full copies of any procedures and protocols referenced in the NSN should be provided, including established published protocols or procedures available in standard reference texts.

If waiver requests were submitted instead of test data to fulfill an information requirement, and therefore test procedures need not be referenced, then this should be specified.

Guidance for non-replicating substances

1. The following information in respect of the micro-organism:

1(a) its identification and the information substantiating its identification

[Note: This information is also required in a CTA or NDS]

The notified substance should be assigned a valid and well-supported taxonomic designation. That taxonomic designation will serve as the cornerstone of the notification and the risk assessment.

The notifier should make a reasonable effort to establish and validate the designation that will be used to identify the substance.

Where the substance has been genetically modified, the identity of the substance should include sources of genetic material and modifications.

Describe the type of bacterium or virus used, its designation including strain or serotype, and the added or deleted gene and its source, if applicable.

For viruses, provide a FASTA format file of the genome of the modified organism.

Also provide a well-documented rationale supporting the claim that the substance will not replicate, and will not revert to replication competence.

1(b) its common and superseded names and any synonyms

[Note: This information is also required in a CTA or NDS]

Provide any common and superseded names for the notified and parental substance/strain as well as its synonyms. All known internal company codes, culture collection designations and synonyms referenced in test study reports or literature should also be provided.

If there are none, then this should be specified.

1(c) its strain history

[Note: This information is also required in a CTA or NDS]

Provide information on the history of the notified substance from its original isolation (environmental/clinical isolate, etc.) until its final development as the notified substance. This information should include:

1. Information and/or copies of any published reports pertaining to the parental and/or notified substance's isolation;
2. A detailed description of the notified substance's development from the parental and ancestral lineages to its current form, and the substance's chain of custody. If available, this should include:
    i. The names of intermediate substances and a description of novel traits;
    ii. Details of previous genetic modifications and/or selection practices, including details of how the modifications were made, the location of these changes (chromosome(s), gene(s) or plasmid(s), and if any introduced DNA is found within a transposable element) and any GenBank records, other than those modifications already described in the section

addressing the description of any modifications to the substance (paragraph 1(d) of Schedule 1); and

iii. All storage and culturing conditions (including the type of media or host cells used for growing the substance).

3. If the notified substance was deposited into one or more culture collection banks, the name of the repository(s) and accession number(s) used (e.g., American Type Culture Collection ATCC 1234).

1(d) a description of any modifications to the micro-organism, including:

1(d)(i) the purpose of the modifications

[Note: This information is also required in a CTA or NDS]

Provide a description of the purpose of each modification made to the substance. If the substance has not been modified, then this should be specified.

1(d)(ii) the methods and steps taken to make the modifications

[Note: This information is also required in a CTA or NDS]

Describe the methods and steps taken to make directed or deliberate modifications to the substance. If the substance has been modified using recombinant DNA or genome editing techniques, the description should include the following:

- cloning strategies and procedures including clearly labeled schematic representations of the modifications made;
- vector construction details (e.g., viruses in gene therapy used to modify cells), and information on the functional elements within the vector and reason(s) for their removal or retention (promoters and other regulatory elements, replication elements, structural genes, selective markers, etc.);
- vector characteristics (shuttle, conjugative, self-transmissible, mobilizable);
- DNA transfer methods employed (conjugation, transformation, transduction, electroporation, microinjection, ballistic injection); and
- the inserted and/or modified sequences or the expression cassette, and in the case of insertions, the copy number of the inserts and/or the copy number of vectors; in the case of deletions, the size of the deleted regions as well as its functional characteristics.

1(d)(iii) the phenotypic and genotypic changes that resulted from the steps referred to in subparagraph 1(d)(ii)

[Note: This information is also required in a CTA or NDS]

Describe changes in physiological characteristics and biological functions known to have resulted from the modifications to the substance. This should also include unintended changes.

The description of genetic changes could be based on:

- restriction enzyme analysis
- restriction map
- nucleic acid hybridization (gene probe) analysis (e.g., Southern Blot analysis)
- PCR

- DNA sequence analysis
- electrophoretic analysis

The description of phenotypic changes should be based on one or more of the following:

- expression of products of inserted genetic material (e.g., Western blot analysis, HPLC, RT-PCR, etc.)
- response in relation to the inserted selection markers, if applicable
- physiological changes based on inserted, modified or deleted genetic material
- flow cytometry data

Provide full copies of all referenced test reports and/or assays.

1(d)(iv) the stability of the changes referred to in subparagraph 1(d)(iii)
[Note: This information is also required in a CTA or NDS]

Describe the stability of the phenotypic and genotypic changes known to have resulted from the modifications to the substance.

The information provided in paragraph 2(f) (shelf life test data) and sub-paragraph 1(d)iii (phenotypic and genotypic changes**)** of Schedule 1 may be referenced.

When using a non-replicating vector, provide information on the screening for absence of replication-competent vector, if applicable.

Provide full copies of all referenced test reports.

1(d)(v) the nature, source and function of any inserted genetic material
[Note: This information is also required in a CTA or NDS]

Describe the nature, source, and function of any genetic material introduced into the substance following modification, by any means, including the:

- size of the introduced genetic material;
- source of any inserted genetic material, including the taxonomic designation of donors;
- functional characteristics of inserted genetic material (for example, regulatory function, origin(s) of replication, coding or non-coding sequences, selection markers, promoter);
- the nucleotide sequence (in FASTA format) or its accession number in a public database and a sequence analysis; and
- copy number and location of inserted genetic material, if applicable.

If no genetic material is inserted, then this should be specified.

1(e) a description of the methods that can be used to distinguish and detect the micro-organism
[Note: This information is also required in a CTA or NDS]

Describe available methods that could be used to detect the substance (for example: in a product or in the environment) and distinguish it from background levels. Information provided in subparagraph 1(d)(iii) of Schedule 1 may be referenced. If no methods exist or none have been developed, a method

should be proposed. Methods described or proposed should be supported by scientific evidence as to their validity.

1(f) a description of the biological and ecological characteristics of the micro-organism, including:

1(f)(i) its life cycle

The following statement may be included to meet the information requirement if it is applicable:

Information on the life cycle is not available given that the notified substance does not replicate.

1(f)(ii) its infectivity, pathogenicity to non-human species, toxicity, and toxigenicity

Provide information on any infectivity or pathogenicity to plants, vertebrate and invertebrate species, as well as any toxicity or toxigenicity associated with the substance (information relating to humans should be provided in paragraph 6(a) of Schedule 1). Information provided should address the following, where applicable:

- ability to colonize;
- ability to infect and the route of infection;
- presence of virulence factors;
- transmission of the substance between hosts;
- involvement of the substance in parasitism or as an obligate or opportunistic pathogen (any disease caused by the substance);
- host range or any biota known to be susceptible to the substance;
- toxin production and conditions under which toxins are produced; and
- any known toxicity related to metabolites produced by the substance.

Pre-clinical data may also be provided to meet the information requirement. Full test reports referenced should be provided.

Literature search terms in combination with the parental or wild-type strain name may include:

"adverse environmental impact*", "adverse effect*", antagonis*, carcinog*, cytotox*, disease*, dispers*, "ecological effect*", genotox*, hazard*, infect*, invasi*, outbreak, opportunistic, pathogen*, phytotoxi*, risk*, toxi*, toxigen*, toxinog*, virul*, disease cycle, population decline, predat*, biocid*, biocontrol

1(f)(iii) its resistance to antibiotics and tolerance to metals and pesticides

Antimicrobial susceptibility (including antibiotic resistance) is addressed in paragraph 6(b) of Schedule 1.

The following statement may be included to meet the information requirement if it is applicable:

The notified substance is intended solely for introduction into the human body, therefore tolerance to metals and pesticides in the environment is not expected.

1(f)(iv) its involvement in biogeochemical cycling

The following statement may be included to meet the information requirement if it is applicable:

The notified substance will have no direct role in the biogeochemical cycling process.

1(f)(v) the conditions required for, and conditions that limit, its survival, growth and replication
[Note: This information is also required in a CTA or NDS]

Information should be provided to describe ranges and optimal conditions for environmental parameters that support survival and replication of the substance, such as:

- pH
- temperature
- salinity
- oxygen and nutrient requirements
- moisture

Describe the substance's susceptibility to disinfectants, physical inactivation parameters (e.g., UV radiation, heat, etc.) and survival outside the host. All claims made should be supported with test data or information from the literature.

1(f)(vi) the mechanisms of its dispersal and the modes of interaction with any dispersal agents
Information should describe the mechanisms of dispersal of the substance in the environment (for example, dispersed by aerosolization, water or animal vectors). Modes of interaction with any dispersal agents such as animal vectors, and the ability to spread to other sites through the method of growth or application, should be provided.

If available, information or data on the potential of the substance to shed from intended hosts should be provided.

Literature search terms in combination with the parental or wild-type strain name may include:

dispers*, fate*, invasi*, spor*, spore, persist*, proliferat*, replicat*, surviv*, spread, climat*

1(g) a description of the mode of action in relation to the intended use
[Note: This information is also required in a CTA or NDS]

Describe the mode of action of the substance in relation to its intended use. The mode of action means the underlying mechanisms through which the substance performs its function (e.g., antigen expression which will induce production of antibodies).

Information collected during product development and efficacy studies, as well as information from a literature search, may fulfill this information requirement. Include pre-clinical and/or clinical trial test data, if available. Provide detailed summaries from the Investigator's Brochure and/or full copies of referenced test reports. A flow diagram may be provided to illustrate the mode of action, if available.

1(h) the identification of any patent or any application for a patent, as the case may be
In the event that the notifier has been granted or have applied for a patent specific to the notified substance or the final product containing the notified substance, in Canada or elsewhere, the following information should be provided:

1. The authority under which the patent was issued or applied for;

2. The patent number or application number; and
3. A copy of the patent, or the patent application, or a web link to the patent.

If no patent has been granted or applied for, this should be indicated.

1(i) the dispersal by gene transfer of traits of pathogenicity to non-human species, toxigenicity and resistance to antibiotics, including a description of:

1(i)(i) the genetic basis for pathogenicity to non-human species, toxigenicity and resistance to antibiotic

For substances that do not contain genes for antimicrobial resistance, infectivity, pathogenicity, toxigenicity or toxicity to non-human species, a statement to this effect may be made with a reference to the genetic modification section (paragraph 1(d) of Schedule 1) and biological and ecological characteristics section (paragraph 1(f)) of Schedule 1) if applicable.

For substances that do contain genes for antimicrobial resistance, infectivity, pathogenicity, toxigenicity or toxicity to non-human species, notifiers should describe them.

This information should contain the following:

- The genes or genomic islands implicated in the pathogenicity to non-human species, toxigenicity, and resistance to antimicrobials, if known, including the number of genes coding for the traits related to pathogenicity, toxigenicity or resistance to antimicrobials, their location (chromosomal or extrachromosomal) and their position;
- If no genes or genomic islands have been reported, this should be indicated.

Literature search terms in combination with the parental or wild-type strain name may include:

adverse effect*, antibiotic*, antifungal*, antiviral*, antimicrobial, gene transfer, transfer, genotox*, hazard*, infect*, invasi*, pathogen*, persist*, resist*, dispers*, toxi*, toxigen*, toxinog*, virul*

1(i)(ii) the capability to transfer genes

Describe the capability for transfer of genetic material from the substance to other organisms, if known. This includes information regarding the presence of mobile genetic elements (e.g., plasmids, transposable elements and integrated viral sequences). Information respecting these genetic elements should include the following:

- size and copy number;
- host range;
- incompatibility group;
- conjugative and mobilization ability;
- insertion specificity; and
- potential for transduction or transposition.

Applicable literature from the previous information requirement subparagraph 1(i)(i) of Schedule 1 may be referred.

1(i)(iii) the conditions that might select for dispersal of traits of pathogenicity to non-human species, toxigenicity and resistance to antibiotics, and whether the conditions are likely to exist at the locations of introduction or within the range of dispersal of the micro-organism
The following statement may be included to meet the information requirement if it is applicable:

There are no known conditions that might exist at the location of introduction or within the range of dispersal that might select for dispersal of traits of pathogenicity to non-human species, toxigenicity or antimicrobial resistance.

1(j) a description of the geographic distribution of the micro-organism
The following statement may be included to meet the information requirement if it is applicable:

The notified substance's geographic distribution is determined by the locations of manufacturing facilities, treatment sites and the humans/hosts/recipients receiving the biologic drug containing the notified substance.

2. The following information in respect of the manufacture and importation of the micro-organism:

2(a) the identification of trade names and manufacturers, importers and vendors
[Note: This information is also required in a CTA or NDS]

Indicate all known or foreseen trade names for the substance, including names previously used to identify the substance or its formulation.

Also indicate the name of the manufacturer of the substance, and if the substance is to be imported into Canada, the names of the importers, and the complete listing of names and addresses of all potential and/or confirmed distribution points (for example, vendors, clinical trial sites, formulators/blenders). If there are no trade names, manufacturers, importers or vendors, then this should be specified.

Provide information related to the clinical trial site(s) and the parameters used to select the location of the clinical trial site(s). If a clinical trial site has not yet been selected, parameters used to select the location of the clinical site will be sufficient to address the information requirement.

2(b) the identification of locations of manufacture in Canada
[Note: This information is also required in a CTA or NDS]

Identify all intended locations (address) of manufacture of the substance in Canada. If there are no manufacturing locations in Canada, this should be specified.

2(c) the physical state of the formulation
[Note: This information is also required in a CTA or NDS]

Describe the physical form of the substance in the formulation (for example, powder, solution or mist).

2(d) the concentration of the micro-organism in the formulation
[Note: This information is also required in a CTA or NDS]

Provide the concentration of the substance in the commercial formulation. Examples of units for concentration that may be used include, but are not limited to:

- colony forming unit per millilitre (CFU/mL) or per gram (CFU/g)
- number of spores per millilitre (Spore/mL) or per gram (Spore/g)
- plaque forming unit per millilitre (PFU/mL) or per gram (PFU/g)
- viral particle per millilitre (VP/mL) or per gram (VP/g)
- fluorescent focus unit per millilitre (FFU/mL) or per gram (FFU/g)
- tissue culture infectious dose (TCID)
- genome copy per millilitre (GC/mL) or per gram (GC/g)
- number of cells per millilitre (cells/mL) or per gram (cells/g)

2(e) the identification and concentration of other ingredients and of any contaminants in the formulation

[Note: This information is also required in a CTA or NDS]

Provide a list of all the components (both active and inactive ingredients) that make up the formulation, including the relative concentration of each ingredient. For example, any substance that is added to the formulation in order to stimulate growth or metabolic activity of the notified substance and any carrier medium should be identified. A certificate of analysis based on representative samples should also be provided.

2(f) the viability of the micro-organism in the formulation

[Note: This information is also required in a CTA or NDS]

Provide the viability and expected shelf life of the substance in the formulation, taking into consideration the recommended storage procedures. Express shelf life as the percentage of viable cells remaining in the formulation after a specific storage period, calculated from the viability at the time of production and the viability at the end of the projected shelf-life. Provide full test reports referenced. If test data is not yet available, then this should be specified.

2(g) a description of any recommended storage and disposal procedures

[Note: This information is also required in a CTA or NDS]

Information on storage procedures should include:

- a description of any recommended storage conditions (e.g., lighting, humidity, temperature, etc.);
- type of containers used to store or transport the substance formulation (e.g., vial, bucket, tote, leak-proof, puncture-resistant, impact resistant, fitted with lids); and
- any recommendations for storage of the end-use product.

Information on disposal procedures should include:

- A description of any recommended disposal procedures of unused portions of substance and its formulation, including those recommended to the end-user, if applicable.

If there are no recommended storage and disposal procedures or if such procedures are not necessary, then this should be specified.

2(h) an estimation of the quantity of the micro-organism that will be imported into or manufactured in Canada, as the case may be

[Note: This information is also required in a CTA or NDS]

Provide an estimate of the quantity of substance to be manufactured or imported, including the quantity manufactured or imported during the first 12 months, and the expected maximum quantity manufactured or imported in any 12-month period during the first three years.

Quantitative units (volume, mass or quantity of the substance) should reflect the physical state of the formulation (for example, CFU, mL for liquids, or g for solids).

The predicted or known number of doses and the concentration of the therapeutic agent in the doses for one treatment (for example, one treatment consists of 4 doses of 10^8 pfus/mL), or the infectious unit per dose of the vaccine, to be imported or manufactured should also be provided. This can be related to the estimated number of participants in the trial, if known.

2(i) a description of the equipment and methods of manufacture and of quality control and quality assurance procedures

[Note: This information is also required in a CTA or NDS]

Describe:

- the equipment used;
- the manufacturing process (e.g., open/closed loop operations);
- the nature of the production process (i.e., batch or continuous);
- scale of the process;
- maintenance of the cell bank;
- culture methods and conditions (e.g., submerged fermentation, media composition, temperature, etc.);
- any containment measures and emergency contingency plans in place;
- waste treatment; and
- long-term storage options (e.g., storage in liquid nitrogen, lyophilisation, etc.).

The description should also include floor plans that indicate the flow of personnel, material and product, and a flow diagram of the manufacturing process identifying the points of entry or exit of all raw materials and waste materials.

Also describe any quality control and assurance procedures used to manufacture the substance such as:

- monitoring results;
- verification of strain integrity (phenotypic and genotypic identity);
- certificate of analysis of the product containing the substance;
- description of batch testing (number, frequency, range and tolerance limits); and
- measurement of contaminants, residues and impurities.

If the substance is imported and not manufactured in Canada, a summary of the method of manufacture including formulation preparation and QA/QC procedures should be provided.

2(j) a description of the location of manufacturing facilities in Canada
[Note: This information is also required in a CTA or NDS]

Describe each manufacturing location in Canada, including the surrounding area and the proximity of each manufacturing location to populated areas, agricultural areas and watercourses.

This description should adequately describe any containment measures in place at the facility and could include the following:

- the layout of the facility (e.g., diagram or schematic);
- a list of personnel and their training;
- a list of material and product flow in the facility;
- a description of containment features (e.g., exhaust filters, closed loop cycling, etc.);
- a description of standard operating procedures which are followed to ensure containment of the substance;
- a description of security measures in place at the facility;
- a description of procedures in place to report accidents at the facility;
- a description of any culture transfers between unit operations;
- a description of procedures for inactivating the substance;
- a description of procedures for the storage and disposal of unused portions of the substance; and
- a description of emergency response measures for handling small and large spills involving the substance.

If there are no locations of manufacture in Canada, then this should be specified.

2(k) a description of the nature of potential releases of the micro-organism from the manufacturing facilities in Canada or from facilities to which the micro-organism will be imported, as the case may be, and the procedures to control releases
[Note: This information is also required in a CTA or NDS]

Describe any intended or potential emissions or releases of the substance, including treated and untreated releases (liquid, solid, gaseous), from the manufacturing facility or the facility to which the substance will be imported, including clinical trial sites.

Estimate the amount of substance and/or metabolites of concern expected to be released in effluents and emissions during batch or continuous operations. The description should include the number of batches to be produced in a year and the volume of the effluent.

Provide a description of any standard operating procedures in place to limit releases from the facility, including any territorial, provincial or municipal regulations or by-laws adhered to, to prevent widespread release.

2(l) a description of the procedures for the treatment and disposal of wastes containing the micro-organism from the manufacturing facilities in Canada
[Note: This information is also required in a CTA or NDS]

Describe the management of wastes from manufacturing facilities. These may be part of quality control and quality assurance procedures already in place at the manufacturing facility. The handling and disposal of waste includes but is not limited to solid wastes (e.g., biomass, gloves, single-use contaminated materials, re-usable contaminated materials, etc.), liquid wastes (e.g., effluents, spent media, samples, etc.) and gaseous exhausts or other emissions. Provide copies of procedures used. Containers used for the storage or transport of waste before disposal should be described (e.g., volume, sealed, leak-proof, labelled, etc.). When waste disposal is outsourced, this should be specified, and information regarding the methods used by the company and location of disposal should be provided. Appropriate municipal and/or provincial regulations regarding disposal should be referenced and followed.

Provide kill rates or other evidence of the efficacy of the treatment methods (physical or chemical) used when describing the treatment procedures for solid, liquid and gaseous wastes. Results may be provided as a certification of analysis, in-house data or information from the literature, and should demonstrate a reduction in the viability or a decrease in the number or concentration of cells, spores, viral particles, etc. This can be expressed as a percentage of reduction in viability of substance for a given method/timeframe or another well-described and relevant unit of measure to demonstrate that the treatment method described is effective.

When municipal, provincial or federal statutes, regulations or by-laws are referenced, provide a copy of the relevant portion. Also provide copies of permits, licences, certificates or any other required approval regarding the discharge or disposal of waste from the manufacturing facility.

Where the notified substance produces secondary metabolites (including toxins) that may be secreted into liquid media or present in wastes, the efficacy of inactivation or containment of those metabolites should be described when discussing the treatment methods and waste disposal procedures.

If there are no procedures in place for the treatment and disposal of wastes or if such procedures are not necessary, then this should be specified.

In the case of import only, provide information on the disposal of contaminated materials and wastes to meet the requirements in paragraphs 3(e) and 3(f) of Schedule 1.

3. The following information in respect of the introduction of the micro-organism:

3(a) the intended and potential uses
[Note: This information is also required in a CTA or NDS]

Describe the substance's intended use, linked to the known mode of action. Information from the clinical trials and from the Investigator's Brochure may be provided, or links to previous sections in the NSN describing the clinical trials may be referenced.

Potential uses may include plans for clinical trials for treatment of other diseases or commercialization of product(s) containing the notified substance.

3(b) the history of use
[Note: This information is also required in a CTA or NDS]

Describe the history of use of the substance in Canada or any other country. Information from previous or on-going clinical trials and/or the Investigator's Brochure may support this information requirement.

3(c) a comparison of the natural habitat of the micro-organism to the habitat at potential locations of its introduction, and the nature of the selection that may operate on the micro-organism at the potential locations of introduction
The following statement may be included to meet the information requirement if it is applicable:

The notified substance is introduced into the human body, which is not readily comparable to natural habitats in the environment.

3(d) a description of procedures for the introduction of the micro-organism, including:

3(d)(i) the method of application
[Note: This information is also required in a CTA or NDS]

Describe the proposed equipment for and methods of application of the substance, including how the substance will be administered to patients.

This should also include:

- the physical form of the substance;
- the nature of the formulation; and
- the method of administration of the formulation.

Also describe any necessary biosafety procedures such as handling precautions and personal protective equipment.

3(d)(ii) the quantity, frequency and duration of application
[Note: This information is also required in a CTA or NDS]

Describe the intended and recommended quantity (number of doses and dose concentration), frequency, and duration of application for the substance.

Provide details of the clinical trial and Investigator's Brochure. For an approved therapeutic product, also provide the treatment dosage and the frequency of the duration of a typical treatment.

3(d)(iii) any activities associated with the introduction
[Note: This information is also required in a CTA or NDS]

Administration of other therapeutic products in relation to the clinical trial or monitoring of patients should be specified, if applicable. A copy of the Product Monograph or any instructions given to the

patients may also be provided, if available. If there aren't any other activities associated with the introduction of the substance, then this should be specified.

3(e) a description of any contingency plans in the event of an accidental release
Describe any contingency plans for handling accidental releases of the substance during its transport, storage, handling, use and disposal. These plans may include any available information on procedures and equipment for decontamination, removal and control, as well as training and criteria for determining when contingency plans should be initiated.

If there are no contingency plans, then this should be specified.

3(f) a description of any recommended procedures for terminating the introduction of the micro-organism
[Note: This information is also required in a CTA or NDS]

Provide information concerning disposal of the unused portion of the substance. This includes information pertaining to the return of the substance or product to the supplier, manufacturer or pharmacy. Also provide any procedures in place or parameters for terminating the clinical trial, and procedures followed to treat and dispose of biohazardous wastes. Indicate whether regional or national regulations are being followed.

If there are no procedures for terminating the introduction of the substance, then this should be specified.

4. The following information in respect of the environmental fate of the micro-organism

4(a) the identification of the plant and animal species likely to be exposed and, if infectivity, pathogenicity to non-human species, toxicity and toxigenicity have been identified under subparagraph 1(f)(ii), the identification of the receptor species likely to be exposed
Either of the following statements may be included to meet the information requirement as applicable:

Given that there is no shedding or intended release of the notified substance to the environment, no plant or animal species are expected to be exposed.

Or

Given that there is shedding or potential release of the notified substance to the environment, any plant or animal species that a treated human comes into contact with in the Canadian environment may potentially be exposed.

4(b) a description of habitats where the micro-organism may persist or proliferate
The following statement may be included to meet the information requirement if it is applicable:

As mentioned in subparagraph 1(f)(v), the notified substance does not replicate or survive outside the human body, therefore it is not expected to persist or proliferate in the environment.

4(c) the estimated quantities of the micro-organism in the air, water and soil at the points of introduction, and the estimated population trends

The following statement may be included to meet the information requirement if it is applicable:

As mentioned in subparagraph 1(f)(v), the notified substance does not replicate or survive outside the human body, therefore it is not expected to persist or proliferate in the environment. Estimates in the environment are therefore not relevant.

4(d) any other information on the environmental fate of the micro-organism

Provide any other known information on the persistence, proliferation, dispersal or any other relevant characteristic to predict the fate of the substance in the environment.

If there is no additional information, then this must be stated or the NSN will be deemed incomplete.

5. The following information in respect of the ecological effects of the micro-organism:

5(a) the data from tests conducted to determine the effects of the micro-organism on:

5(a)(i) aquatic plant, invertebrate and vertebrate species likely to be exposed to it

Provide results from three tests detailing the substance's effects on key aquatic species. This includes tests for each of the following species:

- Aquatic plant species
- Aquatic vertebrate animal species
- Aquatic invertebrate animal species

If a waiver is requested under paragraph 106(8)(a) of the Act in respect of this regulatory requirement, the waiver request should:

- Indicate that a waiver is requested under paragraph 106(8)(a) of the Act to meet the data requirement of subparagraph 5(a)(i) of Schedule 1 of the Regulations.
- Provide a literature search on the parental strain or wild type strain that shows it is toxic or not toxic (select applicable term) to aquatic species, however/and (select applicable term) the notified substance does not replicate or survive outside the human body, therefore it is not expected to be introduced into the environment or to have effects on aquatic species if introduced in the environment.

A literature search on the toxicity of the parental strain or wild type strain should be provided and may include the following search terms:

adverse effect*, ecological effect*, hazard*, infect*, opportunistic, pathogen*, phytotoxi*, toxi*, toxigen*, toxinog*

AND aquatic* OR benthic*

AND vertebrate* OR invertebrate* OR plant* , terrestrial, aquatic, outbreak, plant infect, flora, mollus*, arachnid*, insect*,nematod*, arthropod*, bee*, larva*, coleopter*, worm, amphib*, reptil*, animal*, mammal*, fish

5(a)(ii) terrestrial plant, invertebrate and vertebrate species likely to be exposed to it

Provide results from three tests detailing the substance's effects on key terrestrial species. This includes tests for each of the following species:

- Terrestrial plant species
- Terrestrial vertebrate animal species
- Terrestrial invertebrate animal species

Pre-clinical test data may be submitted to meet the terrestrial vertebrate animal species requirement. Full copies of test reports referenced should be provided.

If a waiver is requested under paragraph 106(8)(a) of the Act in respect of this regulatory requirement, the waiver request should:

- Indicate that a waiver is requested under paragraph 106(8)(a) of the Act to meet the terrestrial plant and terrestrial invertebrate data requirements of subparagraph 5(a)(ii) of Schedule 1 of the Regulations.
- Provide a literature search on the parental strain or wild-type strain that shows it is toxic or not toxic (select applicable term) to terrestrial plant and/or invertebrate species, however/and (select applicable term) the notified substance does not replicate or survive outside the human body, therefore it is not expected to be introduced into the environment or have effects on these species if introduced in the environment.

A literature search on the toxicity of the parental strain or wild type strain should be provided and may include the following search terms:

adverse effect*, ecological effect*, hazard*, infect*, opportunistic, pathogen*, phytotoxi*, toxi*, toxigen*, toxinog*

AND terrestrial* OR benthic*

AND invertebrate* OR plant*, outbreak, plant infect, flora, mollus*, arachnid*, insect*, nematod*, arthropod*, bee*, larva*, coleopter*, worm, amphib*

5(b) the involvement of the micro-organism in adverse ecological effects

The following statement may be included to meet the information requirement if it is applicable:

As mentioned in subparagraph 1(f)(v), the notified substance does not replicate or survive outside the human body, therefore it is not expected to be involved in:

- *any adverse effects related to plants and animals, microbiota, or ecological processes (including physico-chemical effects); and*
- *any other adverse ecological effect not already addressed under any other information requirement.*

5(c) the potential of the micro-organism to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity

The following statement may be included to meet the information requirement if it is applicable:

As mentioned in subparagraph 1(f)(v), the notified substance does not replicate or survive outside the human body; therefore it is not expected to have an adverse environmental impact that could affect the conservation and sustainable use of biological diversity.

6. The following information in respect of the human health effects of the micro-organism:

6(a) any documented involvement of the micro-organism in adverse human health effects and a description of the characteristics of the micro-organism that distinguish it from known pathogens

[Note: This information is also required in a CTA or NDS]

Provide information related to the involvement or the potential involvement of the notified substance in any adverse human health effects (e.g., infections, diseases, symptoms of diseases or conditions, toxic effects, allergic reactions, etc.).

This requirement may be fulfilled by providing a review of the scientific literature and detailing documented involvement or potential involvement of the notified substance and/or suitable surrogate substance in adverse human health effects, or lack thereof, as applicable.

The scientific literature review should indicate the literature search strategy used (keywords and time period) and databases used and should address the following:

- the number of cases reported or incidence in a population;
- demographics of the reported cases (e.g., elderly, children, immuno-compromised individuals, otherwise healthy, etc.);
- the nature and severity of the effects (e.g., superficial, systemic, deep infections, acute, chronic, symptoms, etc.);
- type of exposure leading to the adverse effects; and
- geographic locations where reported cases are prevalent.

Literature search terms to be used in combination with the parental or wild type strain name may include:

adverse effect*, disease*, hazard*, immuno*, allergen*, infect*, invasi*, outbreak, opportunistic, pathogen*, risk*, virul*, resist*, compromis*, chronic, acute, sick*, report*, case report*, hospital, clinical, death, human, health

If the substance or introduced genetic material is not associated with adverse human health effects, provide the scientific literature search strategy (keywords and time period) and databases used, showing that there are no relevant results.

Information and data from previous clinical trials may be provided to satisfy this data requirement. Information and test data described in the Investigator's Brochure may be cited and referenced.

After the end of the assessment period of the NSN:

If new adverse human health effects are reported following the use of the notified substance, then this information must be provided to the NS program as soon as possible after learning of it. The notified substance will be subject to a re-evaluation once the additional information is provided.

6(b) the data from tests of antibiotic susceptibility

If a waiver is requested under paragraph 106(8)(a) of the Act in respect of this regulatory requirement, the waiver request should:

- Indicate that a waiver is requested under paragraph 106(8)(a) of the Act to meet the data requirement of paragraph 6(b) of Schedule 1 of the Regulations.
- Confirm the absence of antimicrobial (antibiotic or antiviral or antifungal) resistance genes as described in paragraph 1(d) of Schedule 1.

Explain why the test is not needed in order to determine whether the substance is toxic or capable of becoming toxic.

6(c) the data from tests of pathogenicity that are valid for related micro-organisms that are pathogenic to humans

[Note: This information is also required in a CTA or NDS]

The data requirement refers to pathogenicity testing performed on the substance to determine its pathogenicity to humans, including infectivity, latency, clearance from tissues and organs, and potential toxicological effects.

Data from pre-clinical and clinical trials may be provided to satisfy this data requirement. Reference may be made to test data described in the Investigator's Brochure. Provide all information necessary for a complete and accurate description of the test procedures and results, and all test data (including supporting raw data) and analysis necessary for the NS program to reach an independent conclusion. Copies of signed certification documents should be provided when claiming any accreditation or certification (such as *Good Laboratory Practice* or *Clinical Laboratory Improvement Amendments*).

If a waiver is requested under paragraph 106(8)(a) of the Act in respect of this regulatory requirement, the waiver request should:

- Indicate that a waiver is requested under paragraph 106(8)(a) of the Act to meet the data requirement of paragraph 6(c) of Schedule 1 of the Regulations.
- Explain why the test is not needed in order to determine whether the substance is toxic or capable of becoming toxic.

6(d) the potential for adverse immunologic reactions in persons exposed to the micro-organism

[Note: This information is also required in a CTA or NDS]

Provide information on the ability of the notified substance to elicit adverse immune reactions (e.g., allergic reactions, delayed hypersensitivity, etc.).

Include details on:

- the type and severity of effect (expected or unexpected);
- the nature of exposure preceding the effect;

- the frequency, duration and severity of the effect;
- a brief description of the clinical methods available to manage the effects, if applicable; and
- the proportion of persons exposed who displayed the reaction.

If information available indicates that no adverse immune reactions are reported in persons exposed to the notified substance, the notifier should still indicate the duration of the potential exposure, the nature of this potential exposure, and the system in place for reporting effects.

Relevant information on immunologic reactions from all pre-clinical and clinical trials should also be provided.

6(e) the estimated number of persons who may become exposed and the degree of their exposure to the micro-organism

Provide an estimate of the number of persons (in occupational settings and in the general public) who may be exposed to the substance in Canada during:

- manufacturing in Canada (including research and development, pilot plant, and commercial production);
- transportation and handling;
- processing;
- storage;
- intended use (e.g., patients, trained nurses, clinicians, patient contacts); and
- disposal, destruction, and recycling.

Also provide:

- the number of clinical trials and the number of participants in each clinical trial (and if future clinical trials are planned, provide an estimated number of trials and an estimated number of participants in each trial);
- information on the incidence of the disease in Canada. For example: “It is estimated that the disease for which this treatment has been developed afflicts 10,000 people per year in Canada”; and
- an estimate of the number of patients who would be expected to receive the substance as part of their treatment should the substance be commercialized.

7. All other information and test data in respect of the micro-organism that permit the identification of hazards to the environment and human health and that are in the person’s possession or to which the person may reasonably be expected to have access

“All other information” refers to any relevant information not already provided as part of a response to an information requirement. This information should include a summary of all other information and test data with respect to the substance that are in the possession of the person (i.e. manufacturer or importer) or to which they may reasonably be expected to have access.

“In the possession of the person (i.e., manufacturer or importer)” means the information in:

- the company’s offices in Canada if the NSN was submitted by a Canadian company; and/or
- the foreign company’s offices if the NSN was submitted by a foreign company through a Canadian Agent.

"To which they may reasonably be expected to have access" means information in any of the company's offices worldwide, or other locations where the notifier can access the information.

A summary of the additional information available should be provided giving sufficient detail regarding methodology and results to permit the NS program to determine the relevance and scientific validity of the information.

The NS program may request to see the available information or a full test report (in the case of test data, including raw data) after reviewing the summaries provided.

Any additional information provided should be relevant to identifying hazards to the environment and human health and relevant to the degree of environmental and human exposure to the substance. This may include, for example:

- Experimental data (including negative and positive results);
- Investigator's Brochure;
- Product Monograph, if available;
- Safety Data Sheet, if available;
- Results of scientific literature searches, including information sources (databases), time period searched, search strategy and terms used;
- Product incident reports or results of studies indicating the risk to employees, consumers, customers, public, or the environment (environmental assessment or environmental fate modelling) that may result from the use of the substance;
- Information and data demonstrating efficacy;
- Risk assessments previously conducted on the notified substance (for example, an environmental risk assessment conducted for another agency).

If there is no information or data other than the information already provided in the NSN, then this should be specified.

8. The identification of other government agencies, either outside or within Canada, that the person has notified of the manufacture or importation of the organism, and the purpose of that notification

Provide any known instance(s) when the manufacture or importation of the substance has been notified to other government agencies, either outside or within Canada, and the purpose of such notification(s).

Include:

1. if known, the identity of the government agency, including the complete name, city and country where the government agency is located; and
2. if known, the government agency's file number, the outcome of the assessment and if applicable, the risk management measures imposed by the agency.

For example:

- a CTA has been submitted to Health Canada; or
- an American supplier has notified the United States Environmental Protection Agency under the provisions of the *Toxic Substances Control Act* (TSCA).

If no other government agency has been notified, this should be specified.

9. A description or specification of the test procedures followed in developing the test data, including the test methods, reference substances and quality control and quality assurance procedures
[Note: This information is also required in a CTA or NDS]

When data is provided to address an information requirement, the test conditions, procedures and protocols used to develop and report the test data should be clearly described. Test conditions and procedures should be consistent with established standard methods.

Clearly indicate the test that was used and its source. Also provide a description of the test procedures, including but not limited to:

- identification of the test substance, including any identification or reference numbers used in the study report;
- description of negative and positive controls used and any other relevant strains used for comparison, if applicable;
- quality control and quality assurance procedures;
- a detailed description of the test procedure followed, referencing any standard tests and identifying any deviations from standard or planned protocols; if the test was conducted according to the practices set out in the "Principles of Good Laboratory Practice (GLP)", the required GLP and Quality Assurance statements and documentation; and
- if the test was conducted according to a specific standard other than GLP, the name and address of the test facility, name of the person responsible for the study and the person's signature, dates on which the study was initiated and completed, and if applicable, certification or accreditation documentation.

Full copies of any procedures and protocols referenced in the NSN should be provided, including established published protocols or procedures available in standard reference texts.

If waiver requests were submitted instead of test data to fulfill an information requirement, and therefore test procedures need not be referenced, then this should be specified.

Guidance for replicating substances

1. The following information in respect of the micro-organism:

1(a) its identification and the information substantiating its identification
[Note: This information is also required in a CTA or NDS]

The notified substance should be assigned a valid and well-supported taxonomic designation. That taxonomic designation will serve as the cornerstone of the notification and the risk assessment.

The notifier should make a reasonable effort to establish and validate the designation that will be used to identify the substance.

Where the substance has been genetically modified, the identity of the substance should include sources of genetic material and modifications.

For viruses, provide a FASTA format file of the genome of the modified organism.

1(b) its common and superseded names and any synonyms

[Note: This information is also required in a CTA or NDS]

Provide any common and superseded names for the notified and parental substance/strain as well as its synonyms. All known internal company codes, culture collection designations and synonyms referenced in test study reports or literature should also be provided.

If there are none, then this should be specified.

1(c) its strain history

[Note: This information is also required in a CTA or NDS]

Provide information on the history of the notified substance from its original isolation (environmental/clinical isolate, etc.) until its final development as the notified substance. This information should include:

1. Information and/or copies of any published reports pertaining to the parental and/or notified substance's isolation;
2. A detailed description of the notified substance's development from the parental and ancestral lineages to its current form, and the substance's chain of custody. If available, this should include:
   i. The names of intermediate substances and a description of novel traits;
   ii. Details of previous genetic modifications and/or selection practices, including details of how the modifications were made, the location of these changes (chromosome(s), gene(s) or plasmid(s), and if any introduced DNA is found within a transposable element) and any GenBank records, other than those modifications already described in the section addressing the description of any modifications to the substance (paragraph 1(d) of Schedule 1); and
   iii. All storage and culturing conditions (including the type of media or host cells used for growing the substance).
3. If the notified substance was deposited into one or more culture collection banks, the name of the repository(s) and accession number(s) used (e.g., American Type Culture Collection ATCC 1234).

1(d) a description of any modifications to the micro-organism, including:

1(d)(i) the purpose of the modifications

[Note: This information is also required in a CTA or NDS]

Provide a description of the purpose of <u>each</u> modification made to the substance. If the substance has not been modified, then this should be specified.

1(d)(ii) the methods and steps taken to make the modifications

[Note: This information is also required in a CTA or NDS]

Describe the methods and steps taken to make directed or deliberate modifications to the substance. If the substance has been modified using recombinant DNA or genome editing techniques, the description should include the following:

- cloning strategies and procedures including clearly labeled schematic representations of the modifications made;
- vector construction details (e.g., viruses in gene therapy used to modify cells), and information on the functional elements within the vector and reason(s) for their removal or retention (promoters and other regulatory elements, replication elements, structural genes, selective markers, etc.);
- vector characteristics (shuttle, conjugative, self-transmissible, mobilizable);
- DNA transfer methods employed (conjugation, transformation, transduction, electroporation, microinjection, ballistic injection); and
- the inserted and/or modified sequences or the expression cassette, and in the case of insertions, the copy number of the inserts and/or the copy number of vectors; in the case of deletions, the size of the deleted regions as well as its functional characteristics.

1(d)(iii) the phenotypic and genotypic changes that resulted from the steps referred to in subparagraph 1(d)(ii)

[Note: This information is also required in a CTA or NDS]

Describe changes in physiological characteristics and biological functions known to have resulted from the modifications to the substance. This should also include unintended changes.

The description of genetic changes could be based on:

- restriction enzyme analysis
- restriction map
- nucleic acid hybridization (gene probe) analysis (e.g., Southern Blot analysis)
- PCR
- DNA sequence analysis
- electrophoretic analysis

The description of phenotypic changes should be based on one or more of the following:

- expression of products of inserted genetic material (e.g., Western blot analysis, HPLC, RT-PCR, etc.)
- response in relation to the inserted selection markers, if applicable
- physiological changes based on inserted, modified or deleted genetic material
- flow cytometry data

Provide full copies of all referenced test reports and/or assays.

1(d)(iv) the stability of the changes referred to in subparagraph 1(d)(iii)

[Note: This information is also required in a CTA or NDS]

Describe the stability of the changes known to result from the modifications over multiple generations.

This should include the following information:

- number of generations used to determine the stability;
- genetic stability (chromosomal integration or episomal maintenance, using DNA analysis) with and without selective pressure;
- inheritance of phenotype through the tested number of generations; and
- a description of the test method including the relevance or acceptability of the number of generations used to determine genetic or phenotypic stability.

Provide full copies of all referenced test reports.

1(d)(v) the nature, source and function of any inserted genetic material
[Note: This information is also required in a CTA or NDS]

Describe the nature, source, and function of any genetic material introduced into the substance following modification, by any means, including the:

- size of the introduced genetic material;
- source of any inserted genetic material, including the taxonomic designation of donors;
- functional characteristics of inserted genetic material (for example, regulatory function, origin(s) of replication, coding or non-coding sequences, selection markers, promoter);
- the nucleotide sequence (in FASTA format) or its accession number in a public database and a sequence analysis; and
- copy number and location of inserted genetic material, if applicable.

If no genetic material is inserted, then this should be specified.

1(e) a description of the methods that can be used to distinguish and detect the micro-organism
[Note: This information is also required in a CTA or NDS]

Describe available methods that could be used to detect the substance (for example: in a product or in the environment) and distinguish it from background levels. Information provided in subparagraph 1(d)(iii) of Schedule 1 may be referenced. If no methods exist or none have been developed, a method should be proposed. Methods described or proposed should be supported by scientific evidence as to their validity.

1(f) a description of the biological and ecological characteristics of the micro-organism, including:

1(f)(i) its life cycle
Provide information describing the life cycle of the parental or wild-type strain with a surrogate organism rationale (see *Surrogate Organism* paragraph in the Guidelines), including, where applicable:

- specific characteristics of all life cycle stages and forms;
- sexual and asexual reproductive cycles;
- relationship with other organisms (e.g., commensal, parasitic, symbiotic);
- mechanisms for surviving biotic or abiotic stresses such as spore, cyst, or biofilm formation.

Literature search terms in combination with the parental or wild-type strain name may include:

dispers*, “life cycle”, life AND cycle, spor*, persist*, proliferate*, replicat* spore, surviv*, disease cycle, biofilm, spread

1(f)(ii) its infectivity, pathogenicity to non-human species, toxicity, and toxigenicity

Provide information on any infectivity or pathogenicity to plants, vertebrate and invertebrate species, as well as any toxicity or toxigenicity associated with the substance (information relating to humans should be provided in paragraph 6(a) of Schedule 1). Information provided should address the following, where applicable:

- ability to colonize;
- ability to infect and the route of infection;
- presence of virulence factors;
- transmission of the substance between hosts;
- involvement of the substance in parasitism or as an obligate or opportunistic pathogen (any disease caused by the substance);
- host range or any biota known to be susceptible to the substance;
- toxin production and conditions under which toxins are produced; and
- any known toxicity related to metabolites produced by the substance.

Pre-clinical data may also be provided to meet the information requirement. Full test reports referenced should be provided.

Literature search terms in combination with the parental or wild-type strain name may include:

“adverse environmental impact*”, “adverse effect*”, antagonis*, carcinog*, cytotox*, disease*, dispers*, “ecological effect*”, genotox*, hazard*, infect*, invasi*, outbreak, opportunistic, pathogen*, phytotoxi*, risk*, toxi*, toxigen*, toxinog*, virul*, disease cycle, population decline, predat*, biocid*, biocontrol

1(f)(iii) its resistance to antibiotics and tolerance to metals and pesticides

Antimicrobial susceptibility (including antibiotic resistance) is addressed in paragraph 6(b) of Schedule 1.

The following statement may be included to meet the information requirement if it is applicable:

The notified substance is intended solely for introduction into the human body, therefore tolerance to metals and pesticides in the environment is not expected.

1(f)(iv) its involvement in biogeochemical cycling

The following statement may be included to meet the information requirement if it is applicable:

The notified substance will have no direct role in the biogeochemical cycling process.

1(f)(v) the conditions required for, and conditions that limit, its survival, growth and replication

[Note: This information is also required in a CTA or NDS]

Information should be provided to describe ranges and optimal conditions for environmental parameters that support survival and replication of the substance, such as:

- pH

- temperature
- salinity
- oxygen and nutrient requirements
- moisture

Describe the substance's susceptibility to disinfectants, physical inactivation parameters (e.g., UV radiation, heat, etc.) and survival outside the host. All claims made should be supported with test data or information from the literature.

1(f)(vi) the mechanisms of its dispersal and the modes of interaction with any dispersal agents
Information should describe the mechanisms of dispersal of the substance in the environment (for example, dispersed by aerosolization, water or animal vectors). Modes of interaction with any dispersal agents such as animal vectors, and the ability to spread to other sites through the method of growth or application, should be provided.

If available, information or data on the potential of the substance to shed from intended hosts should be provided.

Literature search terms in combination with the parental or wild-type strain name may include:

dispers*, fate*, invasi*, spor*, spore, persist*, proliferat*, replicat*, surviv*, spread, climat*

1(g) a description of the mode of action in relation to the intended use
[Note: This information is also required in a CTA or NDS]

Describe the mode of action of the substance in relation to its intended use. The mode of action means the underlying mechanisms through which the substance performs its function (e.g., antigen expression which will induce production of antibodies).

Information collected during product development and efficacy studies, as well as information from a literature search, may fulfill this information requirement. Include pre-clinical and/or clinical trial test data, if available. Provide detailed summaries from the Investigator's Brochure and/or full copies of referenced test reports. A flow diagram may be provided to illustrate the mode of action, if available.

1(h) the identification of any patent or any application for a patent, as the case may be
In the event that the notifier has been granted or have applied for a patent specific to the notified substance or the final product containing the notified substance, in Canada or elsewhere, the following information should be provided:

1. The authority under which the patent was issued or applied for;
2. The patent number or application number; and
3. A copy of the patent, or the patent application, or a web link to the patent.

If no patent has been granted or applied for, this should be indicated.

1(i) the dispersal by gene transfer of traits of pathogenicity to non-human species, toxigenicity and resistance to antibiotics, including a description of:

1(i)(i) the genetic basis for pathogenicity to non-human species, toxigenicity and resistance to antibiotic

For substances that do not contain genes for antimicrobial resistance, infectivity, pathogenicity, toxigenicity or toxicity to non-human species, a statement to this effect may be made with a reference to the genetic modification section (paragraph 1(d) of Schedule 1) and biological and ecological characteristics section (paragraph 1(f)) of Schedule 1) if applicable.

For substances that do contain genes for antimicrobial resistance, infectivity, pathogenicity, toxigenicity or toxicity to non-human species, notifiers should describe them.

This information should contain the following:

- The genes or genomic islands implicated in the pathogenicity to non-human species, toxigenicity, and resistance to antimicrobials, if known, including the number of genes coding for the traits related to pathogenicity, toxigenicity or resistance to antimicrobials, their location (chromosomal or extrachromosomal) and their position;
- If no genes or genomic islands have been reported, this should be indicated.

Literature search terms in combination with the parental or wild-type strain name may include:

adverse effect*, antibiotic*, antifungal*, antiviral*, antimicrobial, gene transfer, transfer, genotox*, hazard*, infect*, invasi*, pathogen*, persist*, resist*, dispers*, toxi*, toxigen*, toxinog*, virul*

1(i)(ii) the capability to transfer genes

Describe the capability for transfer of genetic material from the substance to other organisms, if known. This includes information regarding the presence of mobile genetic elements (e.g., plasmids, transposable elements and integrated viral sequences). Information respecting these genetic elements should include the following:

- size and copy number;
- host range;
- incompatibility group;
- conjugative and mobilization ability;
- insertion specificity; and
- potential for transduction or transposition.

Applicable literature from the previous information requirement subparagraph 1(i)(i) of Schedule 1 may be referred.

1(i)(iii) the conditions that might select for dispersal of traits of pathogenicity to non-human species, toxigenicity and resistance to antibiotics, and whether the conditions are likely to exist at the locations of introduction or within the range of dispersal of the micro-organism

Describe the environmental conditions that may influence gene transfer capability by promoting or mitigating the dispersal of traits of pathogenicity to non-human species, toxigenicity and resistance to antimicrobials. Indicate if these conditions are likely to exist in the location of introduction of the

notified substance.

Applicable literature from the previous information requirement subparagraph 1(i)(i) of Schedule 1 may be referred.

1(j) a description of the geographic distribution of the micro-organism
The following statement may be included to meet the information requirement if it is applicable:

The notified substance's geographic distribution is determined by the locations of manufacturing facilities, treatment sites and the humans/hosts/recipients receiving the biologic drug containing the notified substance.

2. The following information in respect of the manufacture and importation of the micro-organism:

2(a) the identification of trade names and manufacturers, importers and vendors
[Note: This information is also required in a CTA or NDS]

Indicate all known or foreseen trade names for the substance, including names previously used to identify the substance or its formulation.

Also indicate the name of the manufacturer of the substance, and if the substance is to be imported into Canada, the names of the importers, and the complete listing of names and addresses of all potential and/or confirmed distribution points (for example, vendors, clinical trial sites, formulators/blenders). If there are no trade names, manufacturers, importers or vendors, then this should be specified.

Provide information related to the clinical trial site(s) and the parameters used to select the location of the clinical trial site(s). If a clinical trial site has not yet been selected, parameters used to select the location of the clinical site will be sufficient to address the information requirement.

2(b) the identification of locations of manufacture in Canada
[Note: This information is also required in a CTA or NDS]

Identify all intended locations (address) of manufacture of the substance in Canada. If there are no manufacturing locations in Canada, this should be specified.

2(c) the physical state of the formulation
[Note: This information is also required in a CTA or NDS]

Describe the physical form of the substance in the formulation (for example, powder, solution or mist).

2(d) the concentration of the micro-organism in the formulation
[Note: This information is also required in a CTA or NDS]

Provide the concentration of the substance in the commercial formulation. Examples of units for concentration that may be used include, but are not limited to:

- colony forming unit per millilitre (CFU/mL) or per gram (CFU/g)
- number of spores per millilitre (Spore/mL) or per gram (Spore/g)

- plaque forming unit per millilitre (PFU/mL) or per gram (PFU/g)
- viral particle per millilitre (VP/mL) or per gram (VP/g)
- fluorescent focus unit per millilitre (FFU/mL) or per gram (FFU/g)
- tissue culture infectious dose (TCID)
- genome copy per millilitre (GC/mL) or per gram (GC/g)
- number of cells per millilitre (cells/mL) or per gram (cells/g)

2(e) the identification and concentration of other ingredients and of any contaminants in the formulation

[Note: This information is also required in a CTA or NDS]

Provide a list of all the components (both active and inactive ingredients) that make up the formulation, including the relative concentration of each ingredient. For example, any substance that is added to the formulation in order to stimulate growth or metabolic activity of the notified substance and any carrier medium should be identified. A certificate of analysis based on representative samples should also be provided.

2(f) the viability of the micro-organism in the formulation

[Note: This information is also required in a CTA or NDS]

Provide the viability and expected shelf life of the substance in the formulation, taking into consideration the recommended storage procedures. Express shelf life as the percentage of viable cells remaining in the formulation after a specific storage period, calculated from the viability at the time of production and the viability at the end of the projected shelf-life. Provide full test reports referenced. If test data is not yet available, then this should be specified.

2(g) a description of any recommended storage and disposal procedures

[Note: This information is also required in a CTA or NDS]

Information on storage procedures should include:

- a description of any recommended storage conditions (e.g., lighting, humidity, temperature, etc.);
- type of containers used to store or transport the substance formulation (e.g., vial, bucket, tote, leak-proof, puncture-resistant, impact resistant, fitted with lids); and
- any recommendations for storage of the end-use product.

Information on disposal procedures should include:

- A description of any recommended disposal procedures of unused portions of substance and its formulation, including those recommended to the end-user, if applicable.

If there are no recommended storage and disposal procedures or if such procedures are not necessary, then this should be specified.

2(h) an estimation of the quantity of the micro-organism that will be imported into or manufactured in Canada, as the case may be

[Note: This information is also required in a CTA or NDS]

Provide an estimate of the quantity of substance to be manufactured or imported, including the quantity manufactured or imported during the first 12 months, and the expected maximum quantity manufactured or imported in any 12-month period during the first three years.

Quantitative units (volume, mass or quantity of the substance) should reflect the physical state of the formulation (for example, CFU, mL for liquids, or g for solids).

The predicted or known number of doses and the concentration of the therapeutic agent in the doses for one treatment (for example, one treatment consists of 4 doses of 10^8 pfus/mL), or the infectious unit per dose of the vaccine, to be imported or manufactured should also be provided. This can be related to the estimated number of participants in the trial, if known.

2(i) a description of the equipment and methods of manufacture and of quality control and quality assurance procedures

[Note: This information is also required in a CTA or NDS]

Describe:

- the equipment used;
- the manufacturing process (e.g., open/closed loop operations);
- the nature of the production process (i.e., batch or continuous);
- scale of the process;
- maintenance of the cell bank;
- culture methods and conditions (e.g., submerged fermentation, media composition, temperature, etc.);
- any containment measures and emergency contingency plans in place;
- waste treatment; and
- long-term storage options (e.g., storage in liquid nitrogen, lyophilisation, etc.).

The description should also include floor plans that indicate the flow of personnel, material and product, and a flow diagram of the manufacturing process identifying the points of entry or exit of all raw materials and waste materials.

Also describe any quality control and assurance procedures used to manufacture the substance such as:

- monitoring results;
- verification of strain integrity (phenotypic and genotypic identity);
- certificate of analysis of the product containing the substance;
- description of batch testing (number, frequency, range and tolerance limits); and
- measurement of contaminants, residues and impurities.

If the substance is imported and not manufactured in Canada, a summary of the method of manufacture including formulation preparation and QA/QC procedures should be provided.

2(j) a description of the location of manufacturing facilities in Canada
[Note: This information is also required in a CTA or NDS]

Describe each manufacturing location in Canada, including the surrounding area and the proximity of each manufacturing location to populated areas, agricultural areas and watercourses.

This description should adequately describe any containment measures in place at the facility and could include the following:

- the layout of the facility (e.g., diagram or schematic);
- a list of personnel and their training;
- a list of material and product flow in the facility;
- a description of containment features (e.g., exhaust filters, closed loop cycling, etc.);
- a description of standard operating procedures which are followed to ensure containment of the substance;
- a description of security measures in place at the facility;
- a description of procedures in place to report accidents at the facility;
- a description of any culture transfers between unit operations;
- a description of procedures for inactivating the substance;
- a description of procedures for the storage and disposal of unused portions of the substance; and
- a description of emergency response measures for handling small and large spills involving the substance.

If there are no locations of manufacture in Canada, then this should be specified.

2(k) a description of the nature of potential releases of the micro-organism from the manufacturing facilities in Canada or from facilities to which the micro-organism will be imported, as the case may be, and the procedures to control releases
[Note: This information is also required in a CTA or NDS]

Describe any intended or potential emissions or releases of the substance, including treated and untreated releases (liquid, solid, gaseous), from the manufacturing facility or the facility to which the substance will be imported, including clinical trial sites.

Estimate the amount of substance and/or metabolites of concern expected to be released in effluents and emissions during batch or continuous operations. The description should include the number of batches to be produced in a year and the volume of the effluent.

Provide a description of any standard operating procedures in place to limit releases from the facility, including any territorial, provincial or municipal regulations or by-laws adhered to, to prevent widespread release.

2(l) a description of the procedures for the treatment and disposal of wastes containing the micro-organism from the manufacturing facilities in Canada
[Note: This information is also required in a CTA or NDS]

Describe the management of wastes from manufacturing facilities. These may be part of quality control and quality assurance procedures already in place at the manufacturing facility. The handling and disposal of waste includes but is not limited to solid wastes (e.g., biomass, gloves, single-use contaminated materials, re-usable contaminated materials, etc.), liquid wastes (e.g., effluents, spent media, samples, etc.) and gaseous exhausts or other emissions. Provide copies of procedures used. Containers used for the storage or transport of waste before disposal should be described (e.g., volume, sealed, leak-proof, labelled, etc.). When waste disposal is outsourced, this should be specified, and information regarding the methods used by the company and location of disposal should be provided. Appropriate municipal and/or provincial regulations regarding disposal should be referenced and followed.

Provide kill rates or other evidence of the efficacy of the treatment methods (physical or chemical) used when describing the treatment procedures for solid, liquid and gaseous wastes. Results may be provided as a certification of analysis, in-house data or information from the literature, and should demonstrate a reduction in the viability or a decrease in the number or concentration of cells, spores, viral particles, etc. This can be expressed as a percentage of reduction in viability of substance for a given method/timeframe or another well-described and relevant unit of measure to demonstrate that the treatment method described is effective.

When municipal, provincial or federal statutes, regulations or by-laws are referenced, provide a copy of the relevant portion. Also provide copies of permits, licences, certificates or any other required approval regarding the discharge or disposal of waste from the manufacturing facility.

Where the notified substance produces secondary metabolites (including toxins) that may be secreted into liquid media or present in wastes, the efficacy of inactivation or containment of those metabolites should be described when discussing the treatment methods and waste disposal procedures.

If there are no procedures in place for the treatment and disposal of wastes or if such procedures are not necessary, then this should be specified.

In the case of import only, provide information on the disposal of contaminated materials and wastes to meet the requirements in paragraphs 3(e) and 3(f) of Schedule 1.

3. The following information in respect of the introduction of the micro-organism:

3(a) the intended and potential uses

[Note: This information is also required in a CTA or NDS]

Describe the substance's intended use, linked to the known mode of action. Information from the clinical trials and from the Investigator's Brochure may be provided, or links to previous sections in the NSN describing the clinical trials may be referenced.

Potential uses may include plans for clinical trials for treatment of other diseases or commercialization of product(s) containing the notified substance.

3(b) the history of use
[Note: This information is also required in a CTA or NDS]

Describe the history of use of the substance in Canada or any other country. Information from previous or on-going clinical trials and/or the Investigator's Brochure may support this information requirement.

3(c) a comparison of the natural habitat of the micro-organism to the habitat at potential locations of its introduction, and the nature of the selection that may operate on the micro-organism at the potential locations of introduction
The following statement may be included to meet the information requirement if it is applicable:

The notified substance is introduced into the human body, which is not readily comparable to natural habitats in the environment.

3(d) a description of procedures for the introduction of the micro-organism, including:

3(d)(i) the method of application
[Note: This information is also required in a CTA or NDS]

Describe the proposed equipment for and methods of application of the substance, including how the substance will be administered to patients.

This should also include:

- the physical form of the substance;
- the nature of the formulation; and
- the method of administration of the formulation.

Also describe any necessary biosafety procedures such as handling precautions and personal protective equipment.

3(d)(ii) the quantity, frequency and duration of application
[Note: This information is also required in a CTA or NDS]

Describe the intended and recommended quantity (number of doses and dose concentration), frequency, and duration of application for the substance.

Provide details of the clinical trial and Investigator's Brochure. For an approved therapeutic product, also provide the treatment dosage and the frequency of the duration of a typical treatment.

3(d)(iii) any activities associated with the introduction
[Note: This information is also required in a CTA or NDS]

Administration of other therapeutic products in relation to the clinical trial or monitoring of patients should be specified, if applicable. A copy of the Product Monograph or any instructions given to the patients may also be provided, if available. If there aren't any other activities associated with the introduction of the substance, then this should be specified.

3(e) a description of any contingency plans in the event of an accidental release

Describe any contingency plans for handling accidental releases of the substance during its transport, storage, handling, use and disposal. These plans may include any available information on procedures and equipment for decontamination, removal and control, as well as training and criteria for determining when contingency plans should be initiated.

If there are no contingency plans, then this should be specified.

3(f) a description of any recommended procedures for terminating the introduction of the micro-organism

[Note: This information is also required in a CTA or NDS]

Provide information concerning disposal of the unused portion of the substance. This includes information pertaining to the return of the substance or product to the supplier, manufacturer or pharmacy. Also provide any procedures in place or parameters for terminating the clinical trial, and procedures followed to treat and dispose of biohazardous wastes. Indicate whether regional or national regulations are being followed.

If there are no procedures for terminating the introduction of the substance, then this should be specified.

4. The following information in respect of the environmental fate of the micro-organism

4(a) the identification of the plant and animal species likely to be exposed and, if infectivity, pathogenicity to non-human species, toxicity and toxigenicity have been identified under subparagraph 1(f)(ii), the identification of the receptor species likely to be exposed

Either of the following statements may be included to meet the information requirement as applicable:

Given that there is no shedding or intended release of the notified substance to the environment, no plant or animal species are expected to be exposed.

Or

Given that there is shedding or potential release of the notified substance to the environment, any plant or animal species that a treated human comes into contact with in the Canadian environment may potentially be exposed.

4(b) a description of habitats where the micro-organism may persist or proliferate

A description of potential habitats where the substance could persist or proliferate should be provided. Literature search terms in combination with the parental or wild-type strain name may include:

habitat OR surviv* OR growth conditions

Reference to shedding information may be provided.

4(c) the estimated quantities of the micro-organism in the air, water and soil at the points of introduction, and the estimated population trends

Estimated quantities to be introduced into the environment should be provided.

Reference to shedding information may be provided to support this information requirement.

The estimated population trends of the introduced substance in air, water and soil should also be provided. The estimate should indicate whether quantities of the substance are likely to persist above background levels for an extended period of time, and result in elevated or unusual levels of exposure to plants, animals, and humans. This estimate should be based on the following information:

1. the quantity of the substance to be introduced into the environment;

2. the persistence (survival) of the substance in that environment;

3. potential for proliferation of the substance in that environment:

i. conditions for survival, growth and replication;
ii. selection mechanisms;
iii. biological, physical, and chemical factors of the environment (e.g., pH, temperature, salinity); and
iv. any monitoring data.

Persistence (survival) and proliferation data may be obtained from scientific literature. If no relevant data on the notified substance is available from the literature or other sources, sufficient data should be generated to indicate whether populations of the substance will increase, remain the same, or decrease (in air, water, soil) under conditions that simulate those of the intended use.

Literature search terms in combination with the parental or wild-type strain name may include:

persist* OR surviv*

4(d) any other information on the environmental fate of the micro-organism

Provide any other known information on the persistence, proliferation, dispersal or any other relevant characteristic to predict the fate of the substance in the environment.

If there is no additional information, then this must be stated or the NSN will be deemed incomplete.

5. The following information in respect of the ecological effects of the micro-organism:

5(a) the data from tests conducted to determine the effects of the micro-organism on:

5(a)(i) aquatic plant, invertebrate and vertebrate species likely to be exposed to it

Provide results from three tests detailing the substance's effects on key aquatic species. This includes tests for each of the following species:

- Aquatic plant species
- Aquatic vertebrate animal species
- Aquatic invertebrate animal species

The notifier may submit test data on the notified substance or on a surrogate substance (e.g., parental strain or wild type strain) or request a waiver.

5(a)(ii) terrestrial plant, invertebrate and vertebrate species likely to be exposed to it

Provide results from three tests detailing the substance's effects on key terrestrial species. This includes tests for each of the following species:

- Terrestrial plant species
- Terrestrial vertebrate animal species
- Terrestrial invertebrate animal species

Pre-clinical test data may be submitted to meet the terrestrial vertebrate animal species requirement. Full copies of test reports referenced should be provided.

The notifier may submit test data on the notified substance or on a surrogate substance (e.g., parental strain or wild type strain) or request a waiver to meet the terrestrial plant and invertebrate animal species information requirements.

5(b) the involvement of the micro-organism in adverse ecological effects

Provide information indicating the involvement of the substance in adverse ecological effects. This includes any adverse effects related to plants and animals, microbiota, ecological processes (including physico-chemical effects) and any other adverse ecological effect not already addressed under other information requirements. The information that should be provided in this section addresses broad considerations for identifying potential adverse ecological effects.

A literature search on the involvement of the parental strain or wild type strain should be provided and may include the following search terms:

adverse environmental impact*, adverse effect*, disease*, dispers*, ecological effect*, livestock, outbreak, animal, plant, terrestrial, aquatic , persist*, invasiv*, outcompete, population decline, predat*, biocid*, biocontrol

5(c) the potential of the micro-organism to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity

Information already provided in subparagraphs 1(f)(ii), 1(f)(vi), and paragraphs 4(b) and 5(b) of Schedule 1 may be referenced to describe the potential of the substance to adversely affect the sustainable use of biological diversity in resource sectors such as agriculture, fisheries, and forestry. Particular consideration should be given to the potential for adverse effects on threatened and endangered species, and unique and protected ecosystems.

6. The following information in respect of the human health effects of the micro-organism:

6(a) any documented involvement of the micro-organism in adverse human health effects and a description of the characteristics of the micro-organism that distinguish it from known pathogens

[Note: This information is also required in a CTA or NDS]

Provide information related to the involvement or the potential involvement of the notified substance in any adverse human health effects (e.g., infections, diseases, symptoms of diseases or conditions, toxic effects, allergic reactions, etc.).

This requirement may be fulfilled by providing a review of the scientific literature and detailing documented involvement or potential involvement of the notified substance and/or suitable surrogate substance in adverse human health effects, or lack thereof, as applicable.

The scientific literature review should indicate the literature search strategy used (keywords and time period) and databases used and should address the following:

- the number of cases reported or incidence in a population;
- demographics of the reported cases (e.g., elderly, children, immuno-compromised individuals, otherwise healthy, etc.);
- the nature and severity of the effects (e.g., superficial, systemic, deep infections, acute, chronic, symptoms, etc.);
- type of exposure leading to the adverse effects; and
- geographic locations where reported cases are prevalent.

Literature search terms to be used in combination with the parental or wild type strain name may include:

adverse effect*, disease*, hazard*, immuno*, allergen*, infect*, invasi*, outbreak, opportunistic, pathogen*, risk*, virul*, resist*, compromis*, chronic, acute, sick*, report*, case report*, hospital, clinical, death, human, health

If the substance or introduced genetic material is not associated with adverse human health effects, provide the scientific literature search strategy (keywords and time period) and databases used, showing that there are no relevant results.

Information and data from previous clinical trials may be provided to satisfy this data requirement. Information and test data described in the Investigator's Brochure may be cited and referenced.

After the end of the assessment period of the NSN:

If new adverse human health effects are reported following the use of the notified substance, then this information must be provided to the NS program as soon as possible after learning of it. The notified substance will be subject to a re-evaluation once the additional information is provided.

6(b) the data from tests of antibiotic susceptibility

Provide results from antimicrobial susceptibility tests (antibiotic or antiviral or antifungal).

For substances that carry antimicrobial susceptibility or resistance genes (as described in paragraph 1(d) of Schedule 1), full test data reports should be provided.

If a waiver is requested under paragraph 106(8)(a) of the Act in respect of this regulatory requirement and the substance does not carry antimicrobial susceptibility or resistance genes (as described in paragraph 1(d) of Schedule 1), the waiver request should:

- Indicate that a waiver is requested under paragraph 106(8)(a) of the Act to meet the data requirement of paragraph 6(b) of Schedule 1 of the Regulations.
- Confirm the absence of antimicrobial resistance genes as described in paragraph 1(d) of Schedule 1.
- Disclose whether or not antimicrobial treatments are available in the event of infection with the notified substance (describe the treatments, if applicable).

6(c) the data from tests of pathogenicity that are valid for related micro-organisms that are pathogenic to humans

[Note: This information is also required in a CTA or NDS]

The data requirement refers to pathogenicity testing performed on the substance to determine its pathogenicity to humans, including infectivity, latency, clearance from tissues and organs, and potential toxicological effects.

Data from pre-clinical and clinical trials may be provided to satisfy this data requirement. Reference may be made to test data described in the Investigator's Brochure. Provide all information necessary for a complete and accurate description of the test procedures and results, and all test data (including supporting raw data) and analysis necessary for the NS program to reach an independent conclusion. Copies of signed certification documents should be provided when claiming any accreditation or certification (such as *Good Laboratory Practice* or *Clinical Laboratory Improvement Amendments*).

If a waiver is requested under paragraph 106(8)(a) of the Act in respect of this regulatory requirement, the waiver request should:

- Indicate that a waiver is requested under paragraph 106(8)(a) of the Act to meet the data requirement of paragraph 6(c) of Schedule 1 of the Regulations.
- Explain why the test is not needed in order to determine whether the substance is toxic or capable of becoming toxic.

6(d) the potential for adverse immunologic reactions in persons exposed to the micro-organism

[Note: This information is also required in a CTA or NDS]

Provide information on the ability of the notified substance to elicit adverse immune reactions (e.g., allergic reactions, delayed hypersensitivity, etc.).

Include details on:

- the type and severity of effect (expected or unexpected);
- the nature of exposure preceding the effect;
- the frequency, duration and severity of the effect;
- a brief description of the clinical methods available to manage the effects, if applicable; and
- the proportion of persons exposed who displayed the reaction.

If information available indicates that no adverse immune reactions are reported in persons exposed to the notified substance, the notifier should still indicate the duration of the potential exposure, the nature of this potential exposure, and the system in place for reporting effects.

Relevant information on immunologic reactions from all pre-clinical and clinical trials should also be provided.

6(e) the estimated number of persons who may become exposed and the degree of their exposure to the micro-organism

Provide an estimate of the number of persons (in occupational settings and in the general public) who may be exposed to the substance in Canada during:

- manufacturing in Canada (including research and development, pilot plant, and commercial production);
- transportation and handling;
- processing;
- storage;
- intended use (e.g., patients, trained nurses, clinicians, patient contacts); and
- disposal, destruction, and recycling.

Also provide:

- the number of clinical trials and the number of participants in each clinical trial (and if future clinical trials are planned, provide an estimated number of trials and an estimated number of participants in each trial);
- information on the incidence of the disease in Canada. For example: “It is estimated that the disease for which this treatment has been developed afflicts 10,000 people per year in Canada”; and
- an estimate of the number of patients who would be expected to receive the substance as part of their treatment should the substance be commercialized.

7. All other information and test data in respect of the micro-organism that permit the identification of hazards to the environment and human health and that are in the person’s possession or to which the person may reasonably be expected to have access

“All other information” refers to any relevant information not already provided as part of a response to an information requirement. This information should include a summary of all other information and test data with respect to the substance that are in the possession of the person (i.e. manufacturer or importer) or to which they may reasonably be expected to have access.

“In the possession of the person (i.e., manufacturer or importer)” means the information in:

- the company’s offices in Canada if the NSN was submitted by a Canadian company; and/or
- the foreign company’s offices if the NSN was submitted by a foreign company through a Canadian Agent.

“To which they may reasonably be expected to have access” means information in any of the company’s offices worldwide, or other locations where the notifier can access the information.

A summary of the additional information available should be provided giving sufficient detail regarding methodology and results to permit the NS program to determine the relevance and scientific validity of the information.

The NS program may request to see the available information or a full test report (in the case of test data, including raw data) after reviewing the summaries provided.

Any additional information provided should be relevant to identifying hazards to the environment and human health and relevant to the degree of environmental and human exposure to the substance. This may include, for example:

- Experimental data (including negative and positive results);
- Investigator's Brochure;
- Product Monograph, if available;
- Safety Data Sheet, if available;
- Results of scientific literature searches, including information sources (databases), time period searched, search strategy and terms used;
- Product incident reports or results of studies indicating the risk to employees, consumers, customers, public, or the environment (environmental assessment or environmental fate modelling) that may result from the use of the substance;
- Information and data demonstrating efficacy;
- Risk assessments previously conducted on the notified substance (for example, an environmental risk assessment conducted for another agency).

If there is no information or data other than the information already provided in the NSN, then this should be specified.

8. The identification of other government agencies, either outside or within Canada, that the person has notified of the manufacture or importation of the organism, and the purpose of that notification

Provide any known instance(s) when the manufacture or importation of the substance has been notified to other government agencies, either outside or within Canada, and the purpose of such notification(s).

Include:

3. if known, the identity of the government agency, including the complete name, city and country where the government agency is located; and
4. if known, the government agency's file number, the outcome of the assessment and if applicable, the risk management measures imposed by the agency.

For example:

- a CTA has been submitted to Health Canada; or
- an American supplier has notified the United States Environmental Protection Agency under the provisions of the *Toxic Substances Control Act* (TSCA).

If no other government agency has been notified, this should be specified.

9. A description or specification of the test procedures followed in developing the test data, including the test methods, reference substances and quality control and quality assurance procedures
[Note: This information is also required in a CTA or NDS]

When data is provided to address an information requirement, the test conditions, procedures and protocols used to develop and report the test data should be clearly described. Test conditions and procedures should be consistent with established standard methods.

Clearly indicate the test that was used and its source. Also provide a description of the test procedures, including but not limited to:

- identification of the test substance, including any identification or reference numbers used in the study report;
- description of negative and positive controls used and any other relevant strains used for comparison, if applicable;
- quality control and quality assurance procedures;
- a detailed description of the test procedure followed, referencing any standard tests and identifying any deviations from standard or planned protocols; if the test was conducted according to the practices set out in the "Principles of Good Laboratory Practice (GLP)", the required GLP and Quality Assurance statements and documentation; and
- if the test was conducted according to a specific standard other than GLP, the name and address of the test facility, name of the person responsible for the study and the person's signature, dates on which the study was initiated and completed, and if applicable, certification or accreditation documentation.

Full copies of any procedures and protocols referenced in the NSN should be provided, including established published protocols or procedures available in standard reference texts.

If waiver requests were submitted instead of test data to fulfill an information requirement, and therefore test procedures need not be referenced, then this should be specified.