

GUIDANCE DOCUMENT

Plant Molecular Farming (PMF) Applications: Plant-Derived Biologic Drugs for Human Use

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Health Products and Food Branch

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FOREWORD

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

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

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

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

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1. INTRODUCTION

Health Canada is the federal regulatory authority that evaluates the safety, efficacy, and quality of drugs for market authorization in Canada. In this Guidance document, Plant Molecular Farming (PMF) is defined as the use of genetically engineered plant cells, plant tissues, or whole plants for the production of biologic drugs. A plant-derived biologic drug is defined as a Schedule D (biologic) drug manufactured using PMF.

1.1. OBJECTIVE

The objective of this document is to provide guidance regarding the data requirements for plant-derived biologic drug submissions in Canada. The document should enable sponsors to satisfy requirements under the *Food and Drugs Act* and Regulations.

1.2. SCOPE

This Guidance document applies to all biologic human-use drugs, as set out in Schedule D to the *Food and Drugs Act*, that are produced from genetically engineered plant cells, plant tissues, or whole plants. This document is applicable to biologic drugs manufactured using transient or stable expression systems.

This Guidance document does not apply to the following drug products:

- Natural Health Products (NHPs) as defined in the *Natural Health Products Regulations* under the *Food and Drugs Act*;
- Drugs that are produced from plants that are altered through conventional horticulture/breeding practices.

Existing Health Canada and International Conference on Harmonisation (ICH) guidelines for the manufacturing of active ingredients, drug substances, and drug products made by conventional or currently accepted methods (e.g., bacterial and animal cell culture) or production platforms can be applied to the manufacturing steps and process intermediates (e.g., initial extract, drug substance, and drug product) for plant-derived biologic drugs. All of Health Canada's quality, non-clinical, and clinical requirements and considerations for product submission and evaluation are applicable unless otherwise stated.

Only information particular to biologic drugs derived from PMF platforms is addressed in this Guidance document.

Note:

In this document, "sponsor" refers to both product manufacturers/fabricators, and sponsors of regulatory information submitted to Health Canada, as applicable.

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

The content of this document does not intend to cover every conceivable case. Alternate means of complying with the data information outlined can be considered with appropriate scientific justification. Different approaches may be considered as new technologies emerge.

1.3. POLICY STATEMENTS

The following principles guide the request for submission information outlined in this document:

- Plant-derived biologic drugs are subject to the same general submission requirements and same process for obtaining market authorization in Canada as other biologic drugs.
- Health Canada's evaluation of plant-derived biologic drugs is dependent on information that addresses risks unique to PMF production platforms, particularly in the pre-harvest and harvest stages of the production process using whole plants.
- Plant-derived biologic drugs shall meet the same quality and safety standards as drugs produced by conventional production platforms.
- Health Canada is committed to strive for regulatory convergence with other regulatory authorities internationally; specifically, Health Canada's approach to PMF is flexible, not prescriptive, with respect to quality systems.

1.4. OVERSIGHT OF PLANT-DERIVED BIOLOGIC DRUGS IN CANADA

Pre-market evaluation of the safety, quality, and efficacy of plant-derived biologic drugs is the responsibility of Health Canada, in particular, the Biologics and Genetic Therapies Directorate (BGTD). The *Food and Drugs Act* and Regulations are administered in partnership with other areas within Health Canada, like the Marketed Health Products Directorate (MHPD) and the Health Products and Food Branch Inspectorate (HPFBI).

Health Canada (HC), Environment Canada (EC), and the Canadian Food Inspection Agency (CFIA) share **regulatory responsibilities for plant-derived biologic drugs**, based on their differing roles with respect to the production organism (i.e., *how* the plant-derived biologic drug is produced) and the end product (i.e., the plant-derived biologic drug). Sponsors of plant-derived biologic drugs should therefore consult these 3 departments/agencies based on the following considerations:

1. Plant-derived biologic drug

- Health Canada's (HC) Health Products and Food Branch (HPFB) oversees the safety, efficacy, and quality of drugs for market authorization in Canada (applicable legislation is the *Food and Drugs Act* and *Food and Drug Regulations*). A sponsor should contact HC-HPFB as per this Guidance.
- Environment Canada's (EC) and HC's Healthy Environments and Consumer Safety Branch (HECSB) jointly administer the New Substances Program, which oversees the environmental and indirect human health assessment of drugs in Canada (applicable legislation is the *Canadian Environmental Protection Act 1999*, and the *New Substances Notification Regulations (Chemicals and Polymers)*). The PMF drug may require notification prior to import or manufacture above certain trigger quantities. This assessment would be done by the Environmental Assessment Unit (EAU) within the New Substances Assessment and Control Bureau (NSACB) in HC-HECSB. A sponsor should contact the New Substances Program to determine whether and/or when an environmental assessment is required for the PMF drug.

2. PMF production organism

- The Canadian Food Inspection Agency's (CFIA) Plant Biosafety Office (PBO) oversees plants with novel traits (PNT) planted in the environment, including PNTs that produce plant-derived biologic drugs (applicable legislation is the *Seeds Act* and *Seeds Regulations*, or the *Plant Protection Act* and *Plant Protection Regulations*). Additionally, the CFIA's Animal Feed Division regulates the manufacture, sale, and import of livestock feeds in Canada (applicable legislation is the *Feeds Act* and *Feed Regulations*). A sponsor should contact CFIA's PBO when drug manufacturing involves environmental release i.e., import, research field trials, crop residues, and commercial production in fields. A sponsor must contact CFIA's Animal Feed Division if planning on using the PMF crop, in whole or in part, or its by-products, in livestock production in Canada. This also applies to livestock research feeding trials performed in Canada using unapproved feed ingredients.
- EC and HC-HECSB's New Substances Program oversees the environmental and indirect human health assessment of new substances, including plant-based production organisms that fall outside the scope of the *Seeds Act* and *Seeds Regulations* (applicable legislation is the *Canadian Environmental Protection Act 1999*, and the *New Substances Notification Regulations (Organisms)*). A sponsor should contact the New Substances Program prior to import or manufacture of these PMF production organisms, when the drug manufacturing or importation involves plant cells grown in bioreactors or plant tissues grown in-lab.
- HC's Pest Management Regulatory Agency (PMRA) oversees the regulation of pesticides, meaning their approval and registration (applicable legislation is the *Pest Control Products Act*). A sponsor should contact PMRA when drug

manufacturing involves the use of pesticides applied to the crop/plant from which the drug was derived.

In summary, HC-HPFB and the New Substances Program (which is EC and HC-HECSB) are interested in the **drug** derived from the plant, whether it be from cells/tissues/whole plants; CFIA is interested in the **production organisms** (i.e., whole plants) that fall within the scope of the *Seeds Act* and *Seeds Regulations*, the *Plant Protection Act* and *Plant Protection Regulations*, or the *Feeds Act* and *Feed Regulations*; the New Substances Program (which is EC and HC-HECSB) is interested in the **production organisms** (e.g., a plant cell line) that fall outside the scope of the *Seeds Act* and *Seeds Regulations*; and PMRA is interested in the **pesticides** used on the production organism.

Agriculture and Agri-Food Canada, Industry Canada, and Natural Resources Canada do not have direct regulatory authority over plant-derived biologic drugs. However, sponsors of plant-derived biologic drugs are invited to consult these departments for the following:

- Agriculture and Agri-Food Canada (AAFC) provides programs, like the Agri-Innovation Program (AIP), to which companies may wish consider applying to obtain funding to assist with research and development (R&D) or commercial pathway development. AAFC's interest is from an innovation perspective, related to R&D and economic aspects of new agricultural technologies such as PMF, which are an important driver of innovation in the agriculture sector in Canada.
- Industry Canada (IC) works to relay the views and impacts on industry regarding policy and regulatory matters that affect the competitiveness of the life sciences sector. It also acts as a focal point to assist companies in understanding how the government can help support their businesses. IC is involved in PMF-related issues, given the importance of this emerging technology platform for the Canadian drug industry.
- Natural Resources Canada (NRCan) provides advice on the potential use of forest species as platforms for PMF and their impact on the forest sector. NRCan's, more specifically the Canadian Forest Service's, interests are founded in competitiveness and resource sustainability through sector innovation and diversification, by building the bio-economy and by the production of value added products from forest species. NRCan has knowledge and expertise on the ecology, genetics, and productivity of forest species.

See Section 4 for contact information.

2. GUIDANCE FOR IMPLEMENTATION

2.1. GENERAL SUBMISSION INFORMATION

Sponsors are encouraged to consult Health Canada at the pre- Clinical Trial Application and pre- New Drug Submission stages of drug development. See Section 3 for contact information.

2.1.1. New Drug Submission and Clinical Trial Application

The information described in this Guidance document is for New Drug Submissions (NDS). A subset of this information is expected for Clinical Trial Applications (CTA). Refer to key CTA Health Canada Guidance documents (see Section 7 - Appendix A).

- General CTA submission requirements for all biologic drugs are set out in:
 - Division 5 (clinical trials requirements); and
 - Division 4 (biologic-specific requirements) in Part C of the *Food and Drug Regulations*.

- General NDS submission requirements for all biologic drugs are set out in:
 - Division 1 (general requirements);
 - Division 1A (establishment licensing requirements);
 - Division 2 (good manufacturing practices requirements);
 - Division 4 (biologic-specific requirements); and
 - Division 8 (licensing requirements for “new drugs”) in Part C of the *Food and Drug Regulations*.

- The submission processes, review target times, review fees, risk management plans (RMP), adverse drug reaction (ADR) reporting, labelling including product monographs (PM) etc., that apply to biologic drugs also apply to plant-derived biologic drugs. Refer to key Health Canada Guidance documents (see Section 7 - Appendix A).

2.1.2. Common Technical Document format

Health Canada recommends that sponsors submit information in Common Technical Document (CTD) format for both CTA and NDS submissions. To help sponsors, this document recommends both what to put in a submission, and where to put the information in CTD Module format.

- In this Guidance document, Section 2.3 “Quality information” and Section 2.4 “Non-clinical and Clinical information” suggest CTD Modules in which the requested quality, non-clinical, and clinical information may be included. PMF-specific information in other CTD Modules is also acceptable.

As an additional reference tool, all quality, non-clinical, and clinical Guidance sections are cross-referenced in table format to suggested CTD Modules (see Section 8 – Appendix B).

- It is suggested that some sections in CTD Module 3 “Quality” be completed both for the biological starting materials (i.e., from stock to harvest – the “upstream” process) and drug substance (i.e., from harvested plant material to finished drug product – the “downstream” process). In this Guidance document, Section 2.3 “Quality information” suggests these CTD Modules. PMF-specific information in CTD Modules other than those suggested is acceptable.

As an additional reference tool, sections in CTD Module 3 suggested for both upstream and downstream are listed in table format (see Section 9 - Appendix C).

- In the case where sponsors have also notified, registered or filed with other Government of Canada Departments or Agencies (e.g., CFIA, EC) as recommended in Section 1.4 “Oversight of plant-derived biologic drugs in Canada”, it is suggested that sponsors inform Health Canada under CTD Module 1.2.8 “Other Application Information”.

2.2. APPLICATION OF GOOD MANUFACTURING PRACTICES

Plant-derived biologic drugs could be manufactured under various conditions which would involve specific application of Good Manufacturing Practices (GMP) and oversight of Health Canada at different stages of production:

- In a bioreactor, e.g., production in plant cells; or
- In containment, i.e., production in plant tissues (e.g., growth cabinet) or whole plants grown indoors (e.g., research laboratory or greenhouse); or
- In confinement, e.g., production in whole plants outdoors with restrictions (i.e., segregated field). Such restrictions may be both general and species-specific, and include requirements for reproductive isolation, post-harvest land use restrictions, field site monitoring, field size restrictions, and disposal of plant material.

2.2.1. Plant cells grown in bioreactors

Internationally harmonized and recognized guidelines covering the principles of cell banking and associated safety testing and quality control for the manufacture of biologic drugs from animal cell substrates are applicable to PMF platforms using plant cells (see Section 5.1 - References 1, 2, 3). All facilities and processes would be expected to meet GMP standards and direct oversight would be conducted by both HPFBI and BGTD.

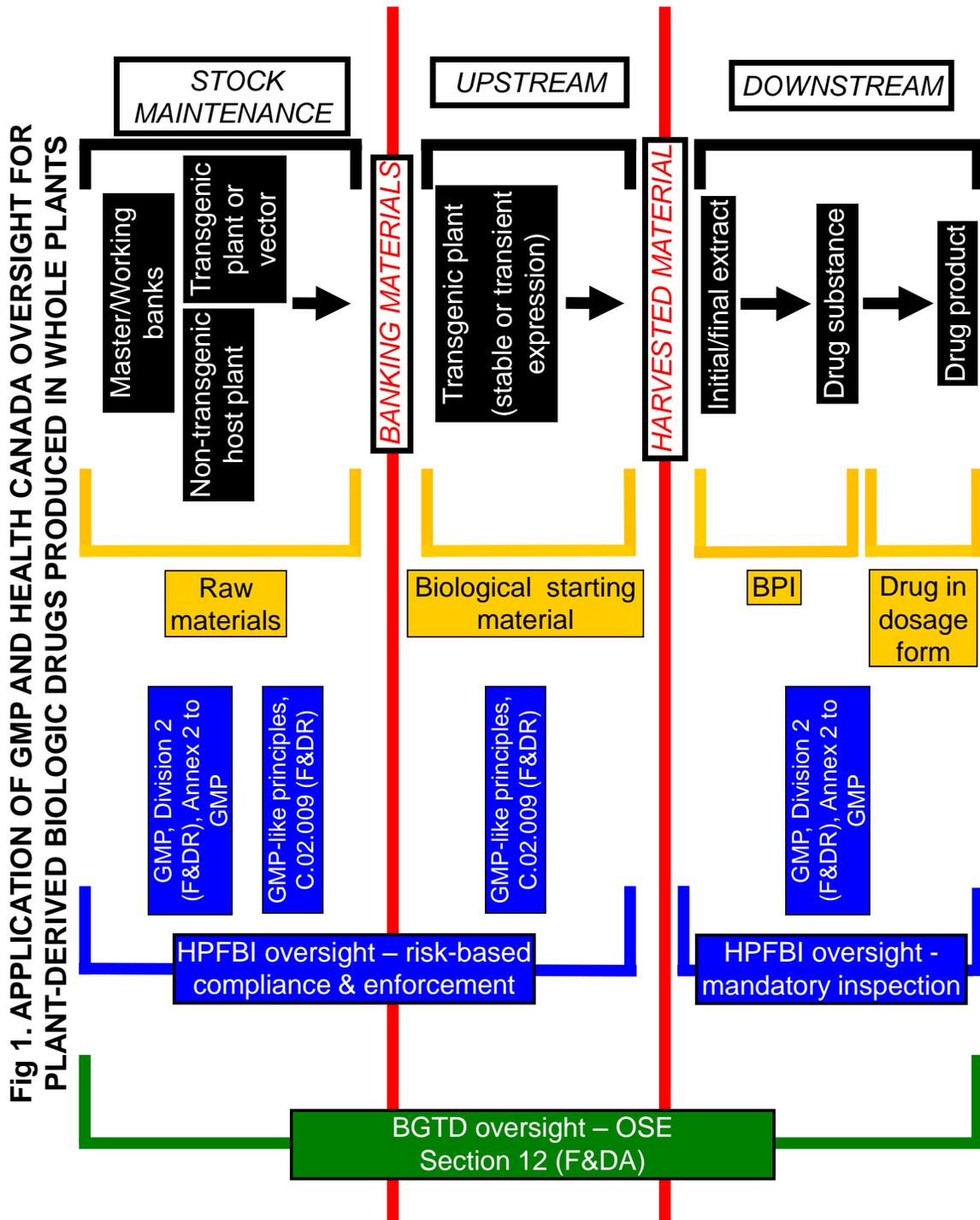
2.2.2. Whole plants or tissues grown in containment or confinement

The regulatory approach for PMF platforms using whole plants divides the manufacturing process into three major phases:

1. the stock maintenance phase;
2. the “upstream” phase (stock to harvest); and
3. the “downstream” phase (harvested plant material to finished drug product).

For the purposes of this document, the division into these phases is based on how GMP applies to the PMF manufacturing processes.

Figure 1 summarizes the application of GMP and Health Canada oversight to the three phases of plant-derived biologic drug manufacturing processes.



Stock maintenance phase

The first phase of PMF production may include the storage and maintenance of banks and/or stocks of transgenic or non-transgenic plants and vectors used to initiate the upstream phase, in either transient or stable expression systems.

At this phase, stock materials, where possible, are expected to be adequately characterized and to meet GMP-like standards (e.g., for the non-transgenic host in transient systems as a raw material) or GMP standards (e.g., for the transgenic stock), as are described for biologic drugs manufactured using conventional platforms (e.g., bacterial or animal cell culture).

The quality considerations of internationally harmonized and recognized guidelines covering the principles of cell banking and associated safety testing for the manufacture of biologic drugs from animal cell substrates may be applicable to the initial phase of PMF platforms using whole plants (see Section 5.1 - References 1, 2, 3).

Where possible, the stock maintenance of master and/or working bank materials is applicable to both stable transgenic or transiently transformed production methods.

Upstream production phase

In the second phase of PMF production, the transgenic plant is considered a biological starting material for the bulk process intermediate. The upstream phase includes all manufacturing operations involving plant cultivation, harvest, and in some cases, initial extraction steps. For most transient expression systems, this phase also includes the transfection process of the host plant.

Health Canada expects adequate sponsor oversight of these process steps in accordance with a defined quality system using the basic concepts of quality assurance, quality control, and GMP (i.e., concepts underlying Division 2 in Part C of the *Food and Drug Regulations*).

Health Canada suggests **adapting basic GMP requirements** (see Section 5.1 – Reference 4), where applicable, to the upstream processes of PMF in order to have a defined quality system employing “**GMP-like principles**”.

The **principles** of monitoring processes and traceability of material at every step (quality assurance), monitoring material with validated tests (quality control), and consistent production and control of materials to meet quality standards (GMP) should be implemented, where applicable, in upstream manufacturing processes. The following are examples to help illustrate how GMP may be applied:

- The GMP basic requirement that *manufacturing processes be clearly defined and controlled to ensure consistency and compliance with approved specifications* may be adapted to the upstream by having controlled processes for the application of pesticides, soil, water, or fertilizer, and for qualification of plant health, height, weight, or other development characteristics.
- Basic concepts of GMP may be applied to the upstream by adapting, for example, the definitions of "batch" and "unsanitary" to a PMF context. Cleaning and facility construction in a greenhouse cannot be considered classical full GMP in a biological production facility. However, the greenhouse area could be "controlled but not classified", terminology which is already used in GMP settings.
- The GMP basic requirement that *critical steps of manufacturing processes and significant changes to the process be validated* should apply to the upstream process i.e., quality attributes and critical process parameters.
- Concepts around premises may not be adaptable to upstream field conditions – e.g. section C.02.004. in the *Food and Drug Regulations* and associated guidance in Health Canada's GMP guidelines and Annex (see Section 7 – under heading *GMP Guidance*). The GMP-like approach applies to seed banks that are maintained for the plants used in transient systems. Such seed banks are not stored or tested as are bacterial or viral seeds, but may be deemed GMP-like for quality control.

Sponsors should demonstrate how quality systems in the upstream process result in the generation of a defined biological starting material suitable for subsequent downstream processing under GMP. Approaches applying GMP-like principles to the upstream process should be supported by appropriate scientific justification and should adhere to Part C, Division 2, section C.02.009 of the *Food and Drug Regulations*.

Downstream production phase

The third phase of PMF production, the downstream phase, includes all drug substance and drug product manufacturing processes. It includes all manufacturing steps from extraction of the active ingredient from the harvested plant material to the finished drug product performed in a **GMP manufacturing facility**.

During the downstream phase, GMP applies to the manufacturing of any bulk process intermediate form of the plant-derived biologic drug and to the manufacturing of the final drug product.

2.3. QUALITY INFORMATION

Production systems utilized for expression of the protein of interest may include fermenter-grown transgenic plant cell cultures, plant tissues, or whole transgenic plants. This section focuses on drugs produced in whole plants that have been bioengineered to produce a recombinant protein. The principles described in this document may also be

applicable to genetically engineered cell or tissue culture production systems derived from plants.

Regardless of the method of gene expression used or the nature of the drug product, submissions for biologic drugs manufactured using such plant expression systems must be well supported with data sufficient to allow an adequate assessment and determination of the product quality.

2.3.1. Plant identification and description

Recommendation – Include information in

- *CTD Module 3.2.S.2.3. Control of Materials (subsection Upstream for biological starting materials)*

A brief description of the host plant should be provided i.e., scientific name, genus, species, sub-species, cultivar/breeding line, common name, with reference to the classification authority, and information on identification of plant species, including data using molecular techniques such as isozyme analysis and DNA fingerprinting.

A brief summary of the reproductive biology of the unmodified plant and its growth characteristics should be included, to indicate, at a minimum, the type of plant according to its growth cycle (annual, perennial, or biennial), breeding system, harvest material, and harvest timing.

During the product development stages, a key consideration may be the selection of the plant species used as the production host for the desired drug product. A scientific rationale and justification should be provided for this selection. In addition, a risk assessment should be presented for all characteristics potentially pharmacologically active in or harmful to humans. Plant species should be assessed, as applicable, for such relevant attributes as:

- growth characteristics and method of plant propagation;
- suitability for routine cultivation;
- susceptibility/resistance to infection with extraneous agents (e.g., plant viruses/viroids, and fungi);
- post-translational modifications (e.g., glycosylation sites, glycan chain structures, absence of relevant animal-specific post-translational modification(s));
- potential for expression of allergenic or toxic compounds;
- presence of compounds exogenous or endogenous to the host plant, and potentially pharmacologically active in or harmful to humans;

- existence of genes in the host plant with known homologies to genes posing potential risks to humans e.g., genes encoding metabolic enzymes producing alkaloids, toxins or anti-nutrients, those encoding potential allergens prompting an autoimmune response; and
- potential for accumulation of any contaminant e.g., heavy metals and pesticides.

All information for assessment, including specific data and literature references, should be provided.

2.3.2. Expression systems

Recommendation – Include information in

- *CTD Module 3.2.S.2.3. Control of Materials (subsection Upstream for biological starting materials)*

The biologic drug of interest can be expressed stably or transiently in the whole plant system, or in specific cells or tissues of the transgenic plant.

2.3.2.1. Stable expression systems

Recommendation – Include information in

- *CTD Module 3.2.S.2.3. Control of Materials (subsection Upstream for biological starting materials)*

Stable expression systems are generally created by unidirectional transfer and incorporation of foreign DNA into plant cells by recombination of specific DNA sequences into the cell genome, with persistence of the gene and its expression in the host in a consistent manner.

Primary transformants are parent plants generated from the initial transformation event. Primary transformants are typically bred through a series of generations to produce stable production transformants with optimized expression. The production transformants are the transgenic plants that are grown during the production process in order to generate the biomass required for subsequent extraction of the active ingredient.

Information regarding expression constructs and vectors used to develop the transformation system should be provided as per the ICH Q5B guideline (see Section 5.1 – Reference 5). This should include detailed information about the promoter and the resulting expression pattern of the gene of interest (e.g., constitutive vs. inducible; tissue- or developmental-specific vs. ubiquitous expression).

A complete description of the transformation, selection, preparation, and establishment of the primary and/or production transformant(s) should be provided. This should include the following information:

- details of all incorporated or modified genetic material, as appropriate, copy number, number of integration sites (if known, the loci), and confirmation of the expected nucleotide sequences;
- pattern and stability of inheritance and expression of the gene(s) of interest. A consistent nomenclature system for plant generations should be applied and explained (e.g., T1, T2.. etc.); and
- information regarding residues of process materials remaining from the transformation (e.g., *Agrobacterium* constituents) .

2.3.2.2. *Transient expression systems*

Recommendation – Include information in

- *CTD Module 3.2.S.2.3. Control of Materials (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.6. Manufacturing Process Development (subsection Upstream for biological starting materials)*

Transient expression systems are those that do not require the stable integration of a foreign gene into the host genome. The inserted genetic material in this process is usually not integrated into the genome of the recipient and may be degraded or diluted through cell division.

Information regarding expression constructs and vectors used to develop the transfection system should be provided as per the ICH Q5B guideline (see Section 5.1– Reference 5). This should include detailed information about the promoter and the resulting expression pattern of the gene of interest (e.g., constitutive vs. inducible; tissue- or developmental-specific vs. ubiquitous expression).

A complete description of the transfection procedure and materials used for the establishment of the developmental, clinical, and commercial scale processes should be provided. This should include the following information:

- identification of any transformant (to include identification of any vector used for the transient expression);
- localization of the expressed protein before extraction (including subcellular targeting);
- determination of the efficiency of transfection in the production plants (e.g., in-process controls);
- determination and qualification of the transient expression time course range (as a process consistency measure);

- consistency of the transfection process (may be demonstrated with end-point measures of the transfected material);
- identification and quantification of residues of process materials from the transformation process (e.g., *Agrobacterium* constituents); and
- maintenance (e.g., storage, stability limits and any requalification) of transfection materials (e.g., expression constructs).

2.3.2.3. Expression and genetic stability at the end of the growth phase

Recommendation – Include information in

- *CTD Module 3.2.S.2.5. Process Validation and/or Evaluation (subsection Upstream for biological starting materials)*

The fidelity of the transgene and its expression during production (e.g., specific sequence and yield) should be monitored when appropriate (e.g., by assessment of plant morphology, biochemical characteristics, etc.). Complete data sets for the analytical measures of genetic stability during the upstream production phase should be generated in later product development phases in both stable and transient expression systems, where applicable.

The results of control testing (functional activity or other determinant characteristic) on later development or production batches should reasonably correlate with the genetic stability and specifications set for the assurance of quality control.

The general principles outlined in the ICH Q5B guideline may be applied with adaptation to the PMF expression system (see Section 5.1 – Reference 5).

2.3.3. Generation of banking systems

Recommendation – Include information in

- *CTD Module 3.2.S.2.3. Control of Materials (subsection Upstream for biological starting materials)*

Acceptable manufacturing practices for biologic drugs from any production platform generally involves the establishment of master and working banks for the provision of consistent and sufficient processing material.

In this Guidance document, the terms Master Bank (MB) and Working Bank (WB) are used to indicate these referenced parental sources. Different materials would be expected to be banked depending on whether a stable or transient expression system is used. For example, a stable expression system would be expected to generate transgenic plant banking materials whereas a transient expression system would be

expected to generate banks of both the host plant and recombinant construct and/or recombinant vector.

Where the source (i.e., host) plant is maintained in other formats (e.g., seed, cultures, etc.), a requalification of the material may be required prior to use in production including identity, quality, and stability indicating parameters.

Such materials should be archived and adequately stored in order to maintain continuity of supply for identical materials over the course of several production runs, and as reference materials for continuous product development.

Containers, storage location and conditions, and shelf life and/or re-test date should be defined based on the stability of the banked material.

Appropriate control measures (e.g., GMP requirements, in-process tests, and if applicable, plant-specific measures) must be implemented for the MB and WB as these measures support the foundation and utility of the production platform. Suitability of these measures is demonstrated by consistency of growth, consistency of production of the intended product, and quality assurance.

The general principles outlined in the ICH Q5D guideline (see Section 5.1 – Reference 3) may be applied, with adaptation to the plant production system.

2.3.4. Upstream production phase (pre-harvest/harvest)

Recommendation – Include information in

- *CTD Module 3.2.S.2.2. Description of Manufacturing Process and Process Controls (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.3. Control of Materials (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.4. Controls of Critical Steps and Intermediates (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.5. Process Validation and/or Evaluation (subsection Upstream for biological starting materials)*

Pre-harvest and harvest steps include all cultivation, collection, and in some cases, initial extraction steps carried out before reception of the biological starting material at the drug substance and/or drug product manufacturing facility. A complete description and annotated flow chart depicting the sequence of production steps should be provided. Reference can be made to the glossary in this Guidance document (see Section 6) or CFIA Guidelines (see Section 5.1 – Reference 6).

Propagation steps and plant cultivation techniques should be described. Depending on the cultivation strategy, duration of the plant growth phase should be clearly defined.

Biotic and abiotic factors that may be critical for controlling production of the intended active ingredient should be identified and investigated during the process development phase. Data should be provided for as many of these factors as possible and any effect on the product's critical quality attributes discussed. Appropriate in-process monitoring should be performed, and operational limits and/or ranges should be created and justified. A clear statement, supported by a scientific rationale, should be provided if no effect is expected or can be demonstrated for any of these abiotic factors.

2.3.4.1. Demonstration of quality system for adequate control

Recommendation – Include information in

- *CTD Module 3.2.A.1. Appendix - Facilities and Equipment (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.A.1. Appendix - Facilities and Equipment (subsection Downstream for drug substance)*

A suitable quality system based on the basic concepts of quality assurance, GMP, and quality control should be established for the upstream production phase. Sponsors should demonstrate how GMP-like principles are met, and specifically identify the actions that were implemented to generate a defined biological starting material.

Ultimately, the pre-harvest and harvest stages of the manufacturing process should be adequately described and controlled (e.g., with application of suitable in-process controls and specifications).

This requirement is intended to establish a well-defined, characterized, and well-documented starting material suitable for subsequent processing under GMP and for the production of a drug product. The operations and the documentation should be available for inspection.

2.3.4.2. Growing strategy

Recommendation – Include information in

- *CTD Module 3.2.S.2.2. Description of Manufacturing Process and Process Controls (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.4. Controls of Critical Steps and Intermediates (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.5. Process Validation and/or Evaluation (subsection Upstream for biological starting materials)*

Sponsors should provide a description of the plant growth phase, including scale, the presence of any soil amendments (e.g., vermiculite) or other additives (e.g., fertilizers, growth factors), major equipment used, light/dark cycles, temperature, humidity, and any other important parameters. Process

controls including in-process tests and operational parameters, with acceptance criteria for process steps and intermediate hold times, should also be provided.

2.3.4.3. Transfection (transient expression systems only)

Recommendation – Include information in

- *CTD Module 3.2.S.2.2. Description of Manufacturing Process and Process Controls (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.2. Description of Manufacturing Process and Process Controls (subsection Downstream for drug substance)*
- *CTD Module 3.2.S.2.3. Control of Materials (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.3. Control of Materials (subsection Downstream for drug substance)*
- *CTD Module 3.2.S.3.2. Impurities (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.3.2. Impurities (subsection Downstream for drug substance)*
- *CTD Module 3.2.S.2.5. Process Validation and/or Evaluation (subsection Upstream for biological starting materials)*

For transient expression systems, the transfection step of the commercial manufacturing process should be described, including preparation of the transfecting materials and criteria for initiation of the transfection process. Appropriate in-process monitoring should be performed, and acceptable operational limits and/or ranges should be established.

Residues of process materials remaining from the transfection process (e.g., *Agrobacterium* constituents) should be quantified, and acceptable operational limits and/or ranges should be created when applicable with appropriate rationale.

2.3.4.4. Monitoring and safeguarding of plant health

Recommendation – Include information in

- *CTD Module 3.2.S.2.2. Description of Manufacturing Process and Process Controls (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.4. Controls of Critical Steps and Intermediates (subsection Upstream for biological starting materials)*

Crop disease may not only result in high levels of plant pathogens in harvested material thus generating contaminants, but may also affect the expression and structure of the drug product. Similarly, plant stress conditions may also affect the quality of the protein of interest.

The quality control system should include procedures for monitoring the status of plant health, for triggering investigations, and for defining actions taken to address these issues.

2.3.4.5. Harvesting (criteria for initiation of harvesting, and controls for personnel, equipment, and facilities)

Recommendation – Include information in

- *CTD Module 3.2.S.2.2. Description of Manufacturing Process and Process Controls (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.4. Controls of Critical Steps and Intermediates (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.5. Process Validation and/or Evaluation (subsection Upstream for biological starting materials)*

The harvesting process should include well-defined criteria for initiation of the harvest, such as stage of development or plant maturity. The use of dedicated equipment is recommended for harvesting the plant material. If the equipment is not dedicated, other uses should be documented, with identification of contact with other plant materials. Appropriate cleaning of the equipment using validated procedures should be performed.

Batch size of the harvested material should be clearly defined and justified. A description of the harvest batch numbering system, including information on any pooling of harvests or intermediates, should be provided.

Traceability of each batch back to the original unit of the MB or WB is essential, and the mechanism established to do this should be described.

Sponsors are encouraged to perform the initial extraction from the plant material in a GMP environment. Regardless of where the initial extraction is carried out, all chemicals that are used during washing and/or extraction, such as disinfectants or organic volatile chemicals, should be removed during downstream process steps in accordance with the ICH Q3C(R5) guideline (see Section 5.1 – Reference 7).

2.3.4.6. Segregation strategy, cleaning, and change-over procedures

Recommendation – Include information in

- *CTD Module 3.2.S.2.2. Description of Manufacturing Process and Process Controls (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.A.1. Facilities and Equipment (subsection Upstream for biological starting materials)*

The risk associated with cross contamination of active ingredients should be addressed and minimized using adequate strategies. Provided that validated change-over procedures are implemented, other crops may be cultivated in areas or with equipment used for the production of plant-derived biologic drugs. The effectiveness of the cleaning procedures for removal of any residues including harvest processing contaminants, by-products and/or cleaning agents, as well as the control of potential microbial contaminants, should be demonstrated.

2.3.4.7. Container closure, conditions, and duration of storage of biological starting materials

Recommendation – Include information in

- *CTD Module 3.2.S.2.2. Description of Manufacturing Process and Process Controls (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.5. Process Validation and/or Evaluation (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.6. Container Closure System (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.7. Stability (subsection Upstream for biological starting materials)*

If the harvested source material is to be stored prior to further processing, specific additional information is required:

- information to demonstrate suitability of the container closure and its components for the intended use;
- description of the storage conditions (e.g., temperature, humidity, volume, density, storage time, etc.);
- appropriate controls of factors which may affect stability, including ability to support growth of microorganisms, residual soil content, presence of foreign material, insects, vermin, etc.; and
- validation of hold times based on (i) the general physicochemical properties of the drug, and (ii) all drug properties that may be reasonably expected to affect material stability and quality.

Source material should be stored under appropriate conditions to ensure that decomposition processes do not increase the concentration of contaminants above specified levels or adversely affect the drug substance, intermediate, or product.

2.3.5. Downstream production phase (post-harvest)

Recommendation – Include information in

- *CTD Module 3.2.S.2.6. Manufacturing Process Development (subsection Downstream for drug substance)*

The overall post-harvest strategy should aim at routinely controlling the quality of each batch of active ingredient produced, and ensuring batch-to-batch consistency. This should take into account the variations inherent in plant-based production.

2.3.5.1. Material transport for processing

Recommendation – Include information in

- *CTD Module 3.2.S.2.5. Process Validation and/or Evaluation (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.5. Process Validation and/or Evaluation (subsection Downstream for drug substance)*

Conditions of transportation should be established to prevent alterations to the physical characteristics of the harvest material and/or potency and/or purity of the active ingredient, as appropriate. Standard operating procedures and records for shipping and receiving should be available, as per Health Canada's GMP guidelines. Reconciliation of the quantities of material after harvest or initial extraction and arriving at the processing facility should be made.

2.3.5.2. Batch definition

Recommendation – Include information in

- *CTD Module 3.2.S.2.2. Description of Manufacturing Process and Process Controls (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.2. Description of Manufacturing Process and Process Controls (subsection Downstream for drug substance)*

The definition of a batch should be provided, and the arrangements for the traceability of each batch back to the original unit of the banking material should be described. Criteria and provisions for any pooling of harvest, or any other intermediates (e.g., initial extract, final extract, process intermediates, drug substance), or final product should be defined.

Where appropriate, in-process control limits should be established and specifications set for chosen critical quality attributes.

2.3.5.3. Purification process and in-process controls

Recommendation – Include information in

- *CTD Module 3.2.S.2.2. Description of Manufacturing Process and Process Controls (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.2. Description of Manufacturing Process and Process Controls (subsection Downstream for drug substance)*

- *CTD Module 3.2.S.2.3. Control of Materials (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.3. Control of Materials (subsection Downstream for drug substance)*
- *CTD Module 3.2.S.2.4. Controls of Critical Steps and Intermediates (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.4. Controls of Critical Steps and Intermediates (subsection Downstream for drug substance)*

The harvest material, initial extract, or final extract used to start the post-harvest manufacturing steps at the drug substance manufacturing facility is considered as the biological starting material. Each batch of the biological starting material should be tested and should comply with pre-established specifications before use in the subsequent processing and purification to drug substance. As an example, material recovery (determination of yield) may be used to demonstrate consistency of the upstream manufacturing phase.

A complete description and annotated flow chart depicting the sequence of production steps which comprise the current manufacturing methods for extraction, concentration, purification, formulation, and filling should be provided.

Sponsors should provide descriptions of any alternate manufacturing method(s) or variation(s), including circumstances of use and rationale (including references to supporting documentation). Manufacturing process development and validation reports, product comparability, etc., should be provided where applicable.

Considering the potential variability inherent in whole plant cultivation, particular attention should be placed on the demonstration of the robustness of the production processes. As is the case with biotechnology-derived drug products, the methods used to purify the product, the in-process controls (allowance for a performance range), and specifications (e.g., purity, potency, mycoplasma, bioburden and adventitious viruses) should be described in detail, justified, and validated.

Potential impurities or contaminants derived from the plant and the production process (e.g., host cell proteins, DNA, plant metabolites, endotoxins, herbicides, fertilizers, and mycotoxins) should be evaluated. Care should be taken to document contaminants which may co-purify with the desired material, and any elements with potential to raise safety concerns (such as hypersensitivity, immunogenicity, and toxicity).

The ability of the purification process to remove impurities and contaminants should be demonstrated and the overall reduction factors for impurities as,

well as reduction factors for each stage of purification, should be established. Where necessary, concentrations of impurities/contaminants higher than expected during normal production (i.e., spiking) should be used to study the robustness of the process for clearing these impurities/contaminants.

2.3.5.4. Consistency of production

Recommendation – Include information in

- *CTD Module 3.2.S.2.5. Process Validation and/or Evaluation (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.2.5. Process Validation and/or Evaluation (subsection Downstream for drug substance)*
- *CTD Module 3.2.S.4.4. Batch Analyses (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.S.4.4. Batch Analyses (subsection Downstream for drug substance)*

Batch-to-batch consistency, with results within established acceptance criteria, should be demonstrated with a statistically justified number of consecutively manufactured batches of harvest material, drug substance, and drug product produced using consecutive cultivations or any other acceptable process validation approach (See Section 5.1 – References 8, 9, 10, 11).

The batch analysis measurements should adequately demonstrate safety and consistency of the cultivation and purification processes for production of the plant-derived biologic drug.

2.3.6. Impurities and potential for allergenicity

Recommendation – Include information in

- *CTD Module 3.2.S.2.4. Controls of Critical Steps and Intermediates (subsection Downstream for drug substance)*
- *CTD Module 3.2.S.3.2. Impurities (subsection Downstream for drug substance)*
- *CTD Module 3.2.S.4. Control of Drug Substance (subsection Downstream for drug substance)*

Characterization of the drug substance to establish a comprehensive quality profile should be carried out with appropriate methods and in accordance with current guidelines, pharmacopoeia, and existing Health Canada requirements.

2.3.6.1. Potential product-related impurities

Recommendation – Include information in

- *CTD Module 3.2.S.3. Characterization (subsection Downstream for drug substance)*
- *CTD Module 3.2.S.3.2. Impurities (subsection Downstream for drug substance)*

- *CTD Module 3.2.S.7. Stability (subsection Downstream for drug substance)*

Appropriate methods should be used to characterize product-related impurities.

For example, this analysis should include the determination of the overall monosaccharide composition, the analysis of oligosaccharides released from the protein (e.g., determination of antennary structures, mapping) and oligosaccharides associated with the protein (e.g., glycosylation per site, glycoform distribution). The impact of the protein's glycosylation on the immunogenicity, the activity, and the *in vivo* half-life of the protein of interest should be determined.

Characterization studies should also include analysis of post-translational modifications other than glycosylation (e.g., acetylation, phosphorylation, and addition of lectins, lipids, polyphenols). Particular attention should be paid to moieties or patterns that are not known to be present in natural human proteins. Where such moieties or patterns are observed, they should be highlighted, and strategies employed to monitor them or to remove them during the purification process should be documented, and adequate results demonstrated.

If there is an inherent degree of structural heterogeneity, for example, due to the presence of post-translationally modified forms, the pattern of heterogeneity should be defined. In addition, the impact of cultivation, harvest, post-harvesting processing, and storage on the pattern of heterogeneity of the active ingredient should be defined in order to establish a basis for an appropriate set of controls and specifications for the drug product, including stability parameters.

2.3.6.2. Potential process-related impurities

Recommendation – Include information in

- *CTD Module 3.2.S.2.5. Process Validation and/or Evaluation (subsection Downstream for drug substance)*
- *CTD Module 3.2.S.3.2. Impurities (subsection Downstream for drug substance)*
- *CTD Module 3.2.S.4.1. Specification (subsection Downstream for drug substance)*

Appropriate methods should be used to characterize process-related impurities. These include, but are not limited to:

- plant proteins other than the transgene-expressed protein (e.g., lectins);
- specific functional proteins (e.g., proteases);

- plant and transient expression vector DNA; and
- secondary plant metabolites such as alkaloids or glycosides endogenous to the transgenic production plants.

In particular, the following should be considered for impurities from the process itself:

- materials employed in production and purification (including soil, fertilizers, pesticides, solvents, chromatographic materials leached from columns, etc.); and
- materials (chemical, biochemical, microbial and/or biological) potentially introduced adventitiously during production and purification (including endotoxins, aflatoxins and other mycotoxins, toxic metals, etc.).

Sponsors should determine the residual level of all potential process-related impurities in the plant material when harvested and which may be present in the final product. Quantitative estimations should be performed using realistic conditions, as well as worst-case scenarios, for the production process.

2.3.6.3. Potential allergenicity of process/product-related impurities

Recommendation – Include information in

- *CTD Module 3.2.S.2.5. Process Validation and/or Evaluation (subsection Downstream for drug substance)*
- *CTD Module 3.2.S.3.2. Impurities (subsection Downstream for drug substance)*
- *CTD Module 3.2.S.4.1. Specification (subsection Downstream for drug substance)*

Plant production systems may contain a number of secondary metabolites (i.e., carotenoids, phytosterols, saponins, glucosinolates, flavenoids, phytoestrogens, protease-inhibitors, terpenes, sulphides, and phytic acids) as well as a variety of host cell proteins, fats, and carbohydrates, which may present some potential risk of allergenicity or other adverse event in the derived drug product.

Impurities should be removed by the purification process to an acceptable level. Where production practices are implemented wherein impurities remain in the finished product (either as quantitatively determined or deemed to be present), a risk assessment analysis should be performed. For any potential allergenic compound, an estimate of the amount per therapeutic dose of drug product should be calculated. Particular attention should be paid to compounds with specific differences in glycan structure caused by differences

in plant and human N-glycan processing (i.e., presence of bisecting $\beta(1,2)$ -xylose and core $\alpha(1,3)$ -fucose residues). A positive-benefit profile must be demonstrated using non-clinical and/or clinical data that assesses the incidence and severity of such events.

Tests for the detection of any potential allergenic compound and quantitation of impurity are determined to be suitable depending upon the selection of method parameters and method validation provided.

2.3.6.4. Risk management

Recommendation – Include information in

- *CTD Module 3.2.S.3.2. Impurities (subsection Downstream for drug substance)*

Where necessary, levels of all residual product- or process-related impurities should be controlled through in-process or batch release specification acceptance criteria, and monitored to establish trends.

A risk analysis shall be performed to determine safety, where necessary.

Sponsors should also specify the maximum amount of any pesticide residues or major pesticide metabolite residues present in the final drug product, and justify the safety of those limits in the context of the indicated use of the drug. Additional pre-clinical studies may be necessary where the safety of any residual level of an impurity in the final drug product may be a concern.

2.3.7. Manufacturing process development

Recommendation – Include information in

- *CTD Module 3.2.S.2.6. Manufacturing Process Development (subsection Upstream for biological starting materials)*

The description of change(s) made to the manufacture of drug substance batches used in support of the submission (e.g., non-clinical or clinical studies) should include changes to the upstream or downstream process or to critical equipment. Changes to the upstream production phase may include, for example, change(s) to the plant cultivation technique, soil amendments, or manufacturing scale. The reason for the change should be explained. The significance of the change should be assessed by evaluating its potential to impact the quality (e.g., biological activity, impurity profile) of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance batches should be provided to determine the impact on quality of the drug substance (see the ICH Q6B guideline for additional guidance, Section 5.1 – Reference 13). A discussion of the data, including a justification for selection of the tests and assessment of results, should be included. When applicable, testing used to assess the impact of manufacturing

changes on the drug substance(s) and the corresponding drug product(s) can also include non-clinical and clinical studies on a case by case basis.

2.3.8. Release testing and specification limits

Recommendation – Include information in

- *CTD Module 3.2.S.2.4. Controls of Critical Steps and Intermediates (subsection Downstream for drug substance)*
- *CTD Module 3.2.S.4.1. Specification (subsection Downstream for drug substance)*
- *CTD Module 3.2.S.4.5. Justification of Specification (subsection Downstream for drug substance)*
- *CTD Module 3.2.P.4.1. Specifications*
- *CTD Module 3.2.P.5.6. Justification of Specification(s)*

A comprehensive quality profile, with appropriate release testing and specification limits, should be in accordance with current Guidance documents, pharmacopoeia, and existing Health Canada requirements e.g., *Guidance Lot Release Program for Schedule D (biologic) Drugs* (see Section 5.1 – Reference 12).

The selection of tests to be included in the specifications should be defined in accordance with the ICH Q6B guideline (see Section 5.1 - Reference 13), and should be based on the complete characterization of the biologic drug.

The rationale used to establish the acceptance criteria should be described, and each criterion should be justified based on characterization data and data obtained from lots used in non-clinical and/or clinical studies.

2.3.9. Control of endogenous and adventitious contaminating agents

Recommendation – Include information in

- *CTD Module 3.2.A.2. Adventitious Agents Safety Evaluation (subsection Upstream for biological starting materials)*
- *CTD Module 3.2.A.2. Adventitious Agents Safety Evaluation (subsection Downstream for drug substance)*

Sponsors should present a risk analysis of the potential for endogenous and adventitious viral and non-viral agents, including those derived from the plant expression system, in the active ingredient. Where it may be relevant on the basis of this analysis, sponsors should propose an integrated step-wise strategy that reliably ensures the safety of each batch of drug product.

Effective strategies, if applicable, are likely to involve but are not limited to, the following measures:

- controls and tests on starting materials, raw materials, reagents, and excipients;

- barriers (containment) applied at the level of agricultural steps (cultivation, harvest, post-harvest processing) aimed at preventing the adventitious entry of extraneous materials and agents;
- *in vitro* and *in vivo* tests to demonstrate the absence of endogenous and adventitious agents at critical production stages (e.g., harvested material and processed bulk); and
- validated virus/viroid inactivation/removal procedures. For additional details, refer to the ICH Q5A(R1) guideline (see Section 5.1 – Reference 14).

Transmissible Spongiform Encephalopathies issues

Sponsors are encouraged to use only TSE-free materials in production of the plant-derived biologic drug.

For drug substances or drug products manufactured with reagents obtained from sources that are at risk of transmitting Transmissible Spongiform Encephalopathies (TSE) agents (e.g., ruminant origin), information and evidence for any potential TSE risk (e.g., name of sponsor, species and tissues from which the material is a derivative, country of origin of the source animals, the material's use and previous acceptance) should be provided where available (See Section 5.1 - Reference 15). At this time, a Certificate of Suitability issued by the European Directorate for the Quality of Medicines (EDQM) is acceptable for raw materials, auxiliary materials, and reagents at risk of transmitting TSE agents (see Section 5.1 – Reference 16). Sponsors are encouraged to contact Health Canada for further guidance.

2.4. NON-CLINICAL AND CLINICAL INFORMATION

2.4.1. Non-clinical

Recommendation – Include information in

- *CTD Module 4.2. Study Reports*
- *CTD Module 4.2.3. Toxicology*
- *CTD Module 4.2.3.7. Other Toxicity Studies (if available)*

Non-clinical evaluation plays an important role in the overall development of plant-derived biologic drugs. Existing guidelines relevant to preclinical development and evaluation of biologic drugs made using other production systems can be applied to plant-derived biologic drugs (see Section 5.2 – References 17, 20, 21, 23).

Generally, proof-of-concept *in vitro* and/or *in vivo* should be demonstrated. The safety studies should define pharmacological and toxicological effects, not only prior to initiation of human studies, but throughout clinical development. The scope of non-clinical studies will be determined by the known attributes of the drug product, including the donor genetic material, the host plant, and the extent of clinical experience of comparable drug products. Early communications are

recommended between the sponsor and Health Canada for agreement on the requirements and type of non-clinical testing.

Additional considerations for the non-clinical study of the plant-derived biologic drugs include the assessment of allergenicity, immunogenicity, and potentially harmful impurities.

2.4.1.1. Toxicity

Recommendation – Include information in

- *CTD Module 4.2.3. Toxicology*

Non-clinical evaluation of toxicity in plant-derived biologic drugs should be similar to that of biologic drugs produced by other production systems. Sponsors should refer to the relevant guidelines for non-clinical information as stated in Section 2.4.1 above. However, special attention should be given to toxicants, pathogens, pesticides (i.e., insecticides, herbicides, and fungicides), pesticide metabolites in the plant, fertilizers, heavy metals, anti-nutrients, and allergens.

Additional pre-clinical studies may be necessary where the safety of any residual level of an impurity (e.g., pesticides and their metabolites) in the final product may be a concern particularly for parenteral drugs, and those which may include repeat dosing and long-term administration. If the host plant is known to contain toxicants (e.g., protease inhibitors, hemolytic agents, neurotoxins, and carcinogens), *in vitro* and animal tests are highly recommended to establish that the toxicant levels are in a safe range in the final drug product. In animal studies, appropriate animal models should be used. Insertion of the transgene can influence the expression of plant toxins or other host proteins, which should be investigated with toxicity studies. Sponsors should also evaluate both the presence and levels of heavy metals (see Quality submission information in Section 2.3), and any potential risks to human health.

Immunotoxicity studies should be performed to investigate the immunotoxic potential of plant-derived biologic drugs if a cause for concern is identified.

2.4.1.2. Immunogenicity

Recommendation – Include information in

- *CTD Module 4.2.3.7. Other Toxicity Studies (if available)*

Immunogenicity testing for plant-derived biologic drugs should be conducted according to existing guidance (see Section 5.2 – Reference 17). Sponsors should give special attention to post-translational modifications unique to plant expression systems, for example, the presence of xylose in glycoproteins and their impact on immunogenicity.

2.4.1.3. Allergenicity

Recommendation – Include information in

- *CTD Module 4.2.3.7. Other Toxicity Studies (if available)*

Allergens may be introduced into the final drug product both from the host plant and from the production process (e.g., from inadvertent contamination with mould, animal dander, animal excrement, or dust mites due to field or storage conditions). Sponsors should assess the need for allergenicity testing for each product on a case-by-case basis. For instance, if a vaccine is produced in the host plant with a potential allergen and the vaccine is adjuvanted to enhance the immune response, the risk of allergenicity might be higher.

If the host plant is known to be a source of allergens, then sponsors should perform appropriate allergenicity testing. Plant-specific modifications should be assessed for potential effects on allergenic responses to the intended drug product.

Sponsors should assess the final drug product for allergenic determinants. For example, allergenicity of the drug can be defined by testing the drug using specific sera derived from patients allergic to the source material.

2.4.2. Clinical

Recommendation – Include information in

- *CTD Module 5. Clinical study reports*

It is highly recommended that during the development of plant-derived biologic drugs, sponsors refer to current guideline(s) related to safety and efficacy which are already in place for other production systems (see Section 5.2 – Reference 24). The pharmacological activity of plant-derived biologic drugs should be well-characterized in clinical studies.

Early communications are highly encouraged between the sponsor and Health Canada for consensus on the submission information to be provided for a specific product.

Glycoproteins produced in plants have unique carbohydrate determinants such as xylose and $\alpha(1,3)$ -fucose, which are not found in mammals. The immunogenicity of the PMF-derived glycoproteins should be addressed in human studies, including immunogenicity and pharmacokinetic/pharmacodynamic (PK/PD) studies, where applicable.

Consistency of final product, dose, and particular dose regimen should be established.

As with other new biologic drugs, a post-marketing Risk Management Plan (RMP) should be provided, including plans for longer-term follow-up of patients for effectiveness and safety.

3. CONTACT INFORMATION - for inquiries regarding drug submissions, adverse drug reactions, inspections

Inquiries and information requests regarding this Guidance document should be communicated to the following areas in Health Canada's Health Products and Food Branch (HC-HPFB):

3.1. SUBMISSION REQUIREMENTS

Office of Regulatory Affairs
Biologics and Genetic Therapies Directorate
Health Products and Food Branch
Health Canada
200 Tunney's Pasture Driveway
Address Locator 0700A
Tunney's Pasture
Ottawa, Ontario
K1A 0K9

“Contact us” webpage: <http://www.hc-sc.gc.ca/contact/dhp-mps/hpfb-dgpsa/bgt-d-pbtg-ora-bar-eng.php>

E-mail: bgt_d_ora@hc-sc.gc.ca or dpbtg_bar@hc-sc.gc.ca

Telephone: 613-957-1722

Fax: 613-946-9520

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

3.2. ADVERSE DRUG REACTION REPORTING

Canada Vigilance Program
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
200 Tunney's Pasture Driveway
Address Locator 0701E
Tunney's Pasture
Ottawa, Ontario
K1A 0K9

“Contact us” webpage: <http://www.hc-sc.gc.ca/contact/dhp-mps/hpfb-dgpsa/cvp-pcv-eng.php>

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

Telephone: 1-866-234-2345 (toll-free)

Fax: 1-866-678-6789 (toll-free)

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

3.3. GMP INSPECTIONS AND ESTABLISHMENT LICENSING REQUIREMENTS

Drug Good Manufacturing Practices Unit
Health Products and Food Branch Inspectorate
Health Products and Food Branch
Health Canada
250 Lanark Avenue
Ottawa, Ontario
K1A 0K9

“Contact us” webpage: <http://www.hc-sc.gc.ca/contact/dhp-mps/hpfb-dgpsa/insp-gmp-bpf-eng.php>

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

Telephone: 613-957-1492

Fax: 613-957-6709

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

3.4. GENERAL QUESTIONS OR COMMENTS ON THIS GUIDANCE

Office of Policy and International Collaboration
Biologics and Genetic Therapies Directorate
Health Products and Food Branch
Health Canada
100 Eglantine Driveway
Address Locator: 0601B
Tunney's Pasture
Ottawa , Ontario
K1A 0K9

“Contact us” webpage: <http://www.hc-sc.gc.ca/contact/dhp-mps/hpfb-dgpsa/opic-bpci-eng.php>

E-mail: BGTD.OPIC@hc-sc.gc.ca or DPBTG.BPCI@hc-sc.gc.ca

Telephone: 613-952-9639

Fax: 613-952-5364

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

Please note that the contact information is correct at the time of writing, and may change over time.

4. CONTACT INFORMATION – for other inquiries

4.1. ENVIRONMENT CANADA AND HEALTH CANADA - NEW SUBSTANCES PROGRAM

New Substances Program

Department of the Environment
Fontaine Building, 8th Floor
200 Sacré-Coeur Blvd.
Gatineau, Quebec
J8X 4C6

“Contact us” webpage: <https://www.ec.gc.ca/subsnouvelles-news/subs/default.asp?lang=En&n=BE3F355A-1>

Email: substances@ec.gc.ca

Telephone: 1-800-567-1999 (toll-free in Canada), 819-953-7156 (outside Canada)

Fax: 819-953-7155

Website: <http://www.ec.gc.ca/subsnouvelles-news/subs>

4.2. CANADIAN FOOD INSPECTION AGENCY

Plant Biosafety Office

Plant Health and Biosecurity Directorate
Policy and Programs Branch
Canadian Food Inspection Agency
59 Camelot Drive
Ottawa, Ontario
K1A 0Y9

“Contact us” webpage: <http://www.inspection.gc.ca/about-the-cfia/contact-us/eng/1299860523723/1299860643049>

Email: pbo@inspection.gc.ca

Telephone: 1-800-442-2342 (CFIA)

Fax: 613-773-7144

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

Animal Feed Division

Canadian Food Inspection Agency
59 Camelot Drive
Ottawa, Ontario
K1A 0Y9

“Contact us” webpage: <http://www.inspection.gc.ca/about-the-cfia/contact-us/eng/1299860523723/1299860643049>

Telephone: 1-800-442-2342 (CFIA)

Fax: 613-773-7565

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

Website: <http://www.inspection.gc.ca>

4.3. PEST MANAGEMENT REGULATORY AGENCY

Pest Management Information Service
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
Address Locator: 6604-E2
Ottawa, Ontario
K1A 0K9

“Contact us” webpage: <http://www.hc-sc.gc.ca/contact/cps-spc/pmra-arla/infoserv-eng.php>

Email: pmra.infoserv@hc-sc.gc.ca

Telephone: 1-800-267-6315 (toll-free in Canada), 1-613-736-3799 (outside Canada, long distance charges apply)

Fax: 613-736-3798

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

Website: <http://www.hc-sc.gc.ca/cps-spc/pest/index-eng.php>

4.4. AGRICULTURE AND AGRI-FOOD CANADA

Agriculture and Agri-Food Canada
Innovation and Growth Policy Division
1341 Baseline Road, Tower 7
Ottawa, Ontario
K1A 0C5

“Contact us” webpage: http://www.agr.gc.ca/index_e.php?s1=help-aide&s2=contact&s3=gen

Telephone: 613-759-1000

Fax: 613-773-2333

4.5. INDUSTRY CANADA

Pharmaceutical Sector Directorate
Manufacturing and Life Sciences Branch
Industry Canada
C.D. Howe Building
235 Queen Street
7th Floor, Room 727E
Ottawa, Ontario
K1A 0H5

“Contact us” webpage: http://www.ic.gc.ca/eic/site/icgc.nsf/eng/h_07026.html

Telephone: 613-954-3077

Fax: 613-954-3107

Teletypewriter: 1-866-694-8389 (Industry Canada)

4.6. NATURAL RESOURCES CANADA

Natural Resources Canada
Canadian Forest Service
Forest Science Division
Science and Program Branch
580 Booth Street
Ottawa, Ontario
K1A 0E4

Telephone: 613-947-9024

Fax: 613-947-9035

Please note that the contact information is correct at the time of writing, and may change over time.

5. REFERENCES

5.1. REFERENCES FOR QUALITY INFORMATION

1. International Conference on Harmonisation (ICH); Q7 Guideline - Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
2. Health Canada; Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)
3. ICH; Q5D Guideline - Derivation and Characterization of Cell Substrates Used for the Production of Biotechnological/Biological Products
4. Health Canada; Good Manufacturing Practices (GMP) Guidelines (GUI-0001)
5. ICH; Q5B Guideline - Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
6. Canadian Food Inspection Agency; Directive Dir2000-07: Conducting Confined Research Field Trials of Plant with Novel Traits in Canada
7. ICH; Q3C(R5) Guideline - Impurities: Guideline for Residual Solvents
8. ICH; Q8(R2) Guideline - Pharmaceutical Development
9. ICH; Q9 Guideline - Quality Risk Management
10. ICH; Q10 Guideline - Pharmaceutical Quality System
11. ICH; Q11 Guideline - Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)
12. Health Canada; Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs.
13. ICH; Q6B Guideline - Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
14. ICH; Q5A(R1) Guideline - Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
15. WHO; WHO Guidelines on Transmissible Spongiform Encephalopathies in relation to Biological and Pharmaceutical Products
16. European Medicines Agency (EMA); Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01 Rev. 3 – July 2011)

5.2. REFERENCES FOR NON-CLINICAL AND CLINICAL INFORMATION

17. ICH; S6(R1) Guideline - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
18. Health Canada website, Consumer Product Safety, Pesticides and Pest Management
19. Health Canada website, Consumer Product Safety, Pesticides and Pest Management, For the Public, Protecting your Health and the Environment, Pesticides and Food, Maximum Residue Limits for Pesticides
20. ICH; M3 Guideline - Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals
21. World Health Organization (WHO); WHO guidelines on nonclinical evaluation of vaccines
22. Pest Management Regulatory Agency (PMRA) of Health Canada website
23. ICH Guidelines in the Safety (“S”) series on the Health Canada website
24. ICH Guidelines in the Efficacy (“E”) series on the Health Canada website

6. GLOSSARY

6.1. ACRONYMS

- AAFC = Agriculture and Agri-Food Canada
- AIP = Agri-Innovation Program
- ADR = Adverse Drug Reaction
- BGTD = Biologics and Genetic Therapies Directorate
- BPI = Bulk Process Intermediate
- CFIA = Canadian Food Inspection Agency
- CTA = Clinical Trial Application
- CTD = Common Technical Document
- EMA = European Medicines Agency
- EAU = Environmental Assessment Unit
- EC = Environment Canada
- FDA = Food and Drug Administration in the United States
- F&DA = *Food and Drugs Act*
- F&DR = *Food and Drug Regulations*
- HC = Health Canada
- HECSB = Healthy Environments and Consumer Branch
- GMP = Good Manufacturing Practices
- HPFBI = Health Products and Food Branch Inspectorate
- ICH = International Conference on Harmonisation
- IC = Industry Canada
- MB = Master Bank
- MHPD = Marketed Health Products Directorate
- NSACB = New Substances Assessment and Control Bureau
- NDS = New Drug Submission

- NHP = Natural Health Product
- NRCan = Natural Resources Canada
- OSE = On-Site Evaluation
- PBO = Plant Biosafety Office
- PK/PD = pharmacokinetic/pharmacodynamic
- PM = Product Monograph
- PMF = Plant Molecular Farming
- PMRA = Pest Management Regulatory Agency
- PNT = Plant with Novel Trait
- R&D = research and development
- RMP = Risk Management Plan
- TSE = Transmissible Spongiform Encephalopathies
- USP = United States Pharmacopoeia
- WB = Working Bank

6.2. DEFINITIONS

- **Adventitious agent (*agent adventice*):** Microorganism (e.g., bacteria, fungi, mycoplasmas, rickettsia, protozoa, parasites, Transmissible Spongiform Encephalopathies (TSE) agents, virus particles) or foreign substitute as per the *United States Food and Drug Administration* (FDA) and the United States Pharmacopoeia (USP) (e.g., chemical or biochemical contaminant) that has been inadvertently introduced into the manufacturing process of a biologic drug, thus requiring non-specific *in vivo* tests, non-specific *in vitro* tests, non-specific biochemical/molecular tests, or specific molecular tests.
- **Biologic drug (*medicament biologique*):** Drugs listed in Schedule D to the *Food and Drugs Act*. Schedule D lists individual products (such as “insulin”), product classes (such as “immunizing agents”), references to particular sources (such as “drugs, other than antibiotics, prepared from microorganisms”), and methodology (such as “drugs obtained by recombinant DNA procedures”). Biologic drugs are derived through the metabolic activity of living organisms and tend to be significantly more variable and structurally complex than chemically synthesized drugs. (from Health Canada’s *Guidance For Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)*)
- **Biological starting material (*matériel biologique de départ*):** Raw material from a biological source which is intended to be used in the fabrication of a drug and from which the active ingredient is derived either directly (e.g., plasma derivatives, ascitic fluid, bovine lung, etc.) or indirectly (e.g., cell substrates, host/vector production cells, eggs, viral strains etc.). (from Health Canada’s *Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs)- GUI-0027*)
- **Bulk Process Intermediate (BPI) (*produit intermédiaire en vrac (PIV)*):** Any intermediate form of a Schedule C or D drug (e.g., final bulk intermediate, bulk material, bulk concentrate, drug substance) which must undergo further processing before it becomes a final product. BPI are usually characterized by a

holding time, storage conditions, and the application of in-process tests. (from Health Canada's *Good Manufacturing Practices (GMP) Guidelines - GUI-0001*)

- **Confinement (*conditions confinées*):** Restrictions that are designed to minimize the exposure of the genetically engineered plant to the environment e.g., the terms and conditions of confinement include, but are not limited to, reproductive isolation, site monitoring, and post-harvest land use restrictions. (slightly modified from the Canadian Food Inspection Agency's *Directive Dir2000-07: Conducting Confined Research Field Trials of Plant with Novel Traits in Canada*)
- **Containment (*isolement*):** Prohibited release of any genetic material into the environment and/or isolation of one or more steps of a manufacturing process (including plant growth and harvest spaces) to prevent contamination of the product or staff, from all other steps of the process.
- **Contaminant (*contaminant*):** A substance ordinarily absent from a material, compound, or environment; or an impurity or adventitious agent, but not an endogenous agent, which may cause an adverse effect.
- **Drug product (dosage form, finished product, final container product) (*produit médicamenteux (forme posologique, produit fini, produit du contenant final)*):** A pharmaceutical product type that contains a biological drug substance, generally in association with excipients. It corresponds to the dosage form in the immediate packaging intended for marketing. (from Health Canada's *Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs)- GUI-0027*)
- **Drug substance (*substance médicamenteuse*):** A defined process intermediate containing the active ingredient, which is subsequently formulated with excipients to produce the drug product. (from Health Canada's *Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs)- GUI-0027*)
- **Endogenous agent (*agent endogène*):** An entity inherent in the host cell, originating, produced, or growing from within a cell, tissue, or organism, that has integrated DNA in the host cell chromosome either expressed in the cell line (transmitted) or not (may include RNA viruses, etc.).
- **Extraneous agent (*agent exogène*):** An entity which should not natively occur in the processing of a material or compound, or in the final material or compound, and is derived or related to some other material or compound which is likely introduced via ancillary means.
- **Good Manufacturing Practices (GMP)-like principles (*principes analogues aux bonnes pratiques de fabrication (BPF)*):** The application of basic concepts of quality assurance, GMP, and quality control to plant molecular farming. For guiding principles, refer to the "GMP basic requirements" in the GMP guidelines in Section 7 - Appendix A.
- **Downstream (phase) (*en aval*):** All drug substance and drug product manufacturing processes, including all manufacturing steps from the harvested plant material/initial extract to the finished drug product, performed in a manufacturing facility subject to GMP requirements.

- **Genetically engineered (*génétiquement modifié*)**: Plant or part thereof contains either a stably- or transiently-expressed recombinant nucleic acid (RNA or DNA) construct.
- **Harvested material (*matériel récolté*)**: Host plants or parts of the host plants, which may contain the active ingredient, used as a biological starting material, collected and preserved for extraction.
- **Host plant (*plante hôte*)**: The parent or originating / source plant (including a tissue or seed) utilized for the production of plant-derived biologic drugs, prior to the introduction/insertion/integration of the gene(s) encoding for biologic drug expression
- **Impurity (*impureté*)**: Any substance present which may arise during synthesis, purification and storage and considered to be different than the chemical composition of a desired material or compound which affects the purity of the desired material or compound (e.g., polymorphic forms, enantiomeric impurities). Please additionally refer to the ICH Q3A(R2) guideline (*Impurities in New Drug Substances*), which sets out chemistry and safety aspects for impurities in new drug substances as (1) organic, either process and drug-related (from starting materials, by-products, intermediates, degradation products, reagents, ligands, catalysts); or (2) inorganic (reagents, ligands, catalysts, heavy metals, residual metals, salts, other process materials); or (3) residual solvents (organic or inorganic liquids as state/transfer vehicles).
- **Locus (plural - loci) (*locus*)**: Specific location of the insert on the DNA of the host plant.
- **Master bank (MB) (*banque primaire*)**: A collection of plant seeds, whole plants or part thereof, tissues, cells or vectors that is homogeneous in genetic make-up which may contain modified genome due to the insertion of gene(s) (i.e., transgenic host plant) or may not contain modified genome (i.e., non-transgenic host plant).
- **Pesticide or pest control product (*pesticide ou produit antiparasitaire*)**:
 - (a) a product, an organism or a substance, including a product, an organism or a substance derived through biotechnology, that consists of its active ingredient, formulants and contaminants, and that is manufactured, represented, distributed or used as a means for directly or indirectly controlling, destroying, attracting or repelling a pest or for mitigating or preventing its injurious, noxious or troublesome effects;
 - (b) an active ingredient that is used to manufacture anything described in paragraph (a); or
 - (c) any other thing that is prescribed to be a pest control product.(from the *Pest Control Products Act*)
- **Plant-derived biologic drug (*médicament dérivé de MCV*)**: Schedule D (biologic) drug manufactured using plant molecular farming.
- **Plant Molecular Farming (PMF) (*moléculture végétale (MCV)*)**: The use of genetically engineered plant cells, plant tissues, or whole plants for the production of biologic drugs.
- **Plant with Novel Traits (PNT) (*végétal à caractère nouveau (VCN)*)**: Plant into which a trait has been intentionally introduced that is new to plants of the

same species cultivated in Canada and has the potential to affect the specific use and safety of the plant with respect to the environment and human health. (from Canadian Food Inspection Agency's *Directive Dir2000-07: Conducting Confined Research Field Trials of Plant with Novel Traits in Canada*)

- **Raw Material (*matière première*)**: Any substance, other than in-process drug or packaging material, intended to be used in the manufacture of drugs, including those that appear in the master formula but that do not appear in the drug such as solvents and processing aids. (from Health Canada's *Good Manufacturing Practices (GMP) Guidelines - GUI-0001*)
- **Schedule D (biologic) drug (*médicament (biologique) de l'annexe D*)**: see definition of "Biologic drug".
- **Specification (*spécifications*)**: A detailed description of a drug, the raw material used in a drug, or the packaging material for a drug, and includes:
 - (a) a statement of all properties and qualities of the drug, raw material or packaging material that are relevant to the manufacture, packaging, and use of the drug, including the identity, potency, and purity of the drug, raw material, or packaging material;
 - (b) a detailed description of the methods used for testing and examining the drug, raw material, or packaging material; and
 - (c) a statement of tolerances for the properties and qualities of the drug, raw material, or packaging material.(from Health Canada's *Good Manufacturing Practices (GMP) Guidelines - GUI-0001, which is the same as section C.02.002. in the Food and Drug Regulations*)
- **Stable expression system (*système d'expression stable*)**: The expression system in which the recombinant DNA is incorporated in the host cell, and is carried and expressed over many generations of the host plant.
- **Stock maintenance (*maintenance du stock*)**: The banking, storage, and testing of any biological materials used to initiate the upstream phase e.g., host plants (for transient systems), transgenic host plants (for stable systems), vectors (for transient systems).
- **Transformant (*transformant*)**: a cell, tissue, or plant that has been altered through the uptake of foreign nucleic acid.
- **Transformation (*transformation*)**: A process of directed modification (as a qualitative/quantitative change) of the content/character of the genetic information of a cell or bacterium by the transfer, uptake and incorporation or integration, of genetic information (as non-native, exogenous DNA), via any of several means (introduction, substitution, viral infection, whole nuclei transplant, cell hybrid transplants, etc.)
- **Transgenic plant(s) or parts thereof (*plante transgénique ou parties de celle-ci*)**: A plant or part of the plant that has been transformed and contains an inserted recombinant DNA construct.
- **Transient expression system (*système d'expression transitoire*)**: The expression system in which the recombinant DNA may or may not be integrated in the host cell DNA, and is expressed only for one generation and not over many generations of the host plant

- **Transmissible Spongiform Encephalopathies (TSE) (*encéphalopathie spongiforme transmissible (EST)*):** All progressive neurodegenerative disorders caused by prions in animals and humans that produce spongiform changes in the brain. For example, bovine spongiform encephalopathy (BSE), chronic wasting disease (CWD), feline spongiform encephalopathy, transmissible mink encephalopathy and scrapie are prion diseases which affect animals. Creutzfeldt-Jakob disease (CJD), variant Creutzfeldt-Jakob disease (vCJD), Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia and Kuru are prion diseases which affect humans.
- **Upstream (phase) (*en amont*):** PMF manufacturing phases involving plant cultivation and growth. These early process steps include all the pre-harvest and harvest manufacturing steps, except for stock (banking materials) production.
- **Working Bank (WB) (*banque de travail*):** Expansion of a portion of the MB, and used to begin the manufacture of individual production batches.

7. APPENDIX A: KEY HEALTH CANADA GUIDANCE DOCUMENTS

Sponsors should refer to the most up-to-date versions of the following key Health Canada Guidance documents. This list is provided as a starting point to help sponsors, and is not exhaustive.

GENERAL GUIDANCE

- Guidance for Industry: Management of Drug Submissions
- Guidance Document: Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format
- Guidance for Industry: Preparation of Drug Submissions in Electronic Common Technical Document (eCTD) Format

CTA GUIDANCE

- Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications
- Guidance Document: Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines - Drugs Used In Clinical Trials (GUI-0036)

GMP GUIDANCE

- Good Manufacturing Practices (GMP) Guidelines (GUI-0001)
- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines - Schedule D Drugs (Biological Drugs) (GUI-0027)
- Guidance on Evidence to Demonstrate Drug GMP Compliance of Foreign Sites (GUI-0080)
- Guidance on Drug Establishment Licences and Drug Establishment Licensing Fees (GUI-0002)
- Drug Establishment Licence Application: Forms and Instructions (FRM-0033)

NDS GUIDANCE

- Guidance for Industry: Drug Name Review - Look-alike Sound-alike (LA/SA) Health Product Names
- Guidance for Industry: Product Monograph
- Guidance for Industry: Product Monograph Appendix I - Product Monograph Template - Schedule D
- Guidance Document: Fees for the Review of Drug Submissions and Applications
- Notice Regarding Implementation of Risk Management Planning including the adoption of International Conference on Harmonisation (ICH) Guidance Pharmacovigilance Planning - ICH Topic E2E

Quality-specific guidance

- Guidance for Industry: Preparation of the Quality Information for Drug Submissions in the CTD Format - Conventional Biotherapeutic Products

- Guidance for Industry: Preparation of the Quality Information for Drug Submissions in the CTD Format - Biotechnological/Biological (Biotech) Products
- Guidance for Industry: Preparation of the Quality Information for Drug Submissions in the CTD Format - Vaccines
- Guidance for Industry: Preparation of the Quality Information for Drug Submissions in the CTD Format - Blood Products

POST-MARKET GUIDANCE

- Guidance Document - Post-Notice of Compliance (NOC) Changes: Framework Document
- Guidance Document - Post-Notice of Compliance (NOC) Changes: Quality Document
- Guidance Document - Post-Notice of Compliance (NOC) Changes: Safety and Efficacy Document
- Guidance for Industry: Drug Name Review - Look-alike Sound-alike (LA/SA) Health Product Names
- Guidance Document for Industry: Reporting Adverse Reactions to Marketed Health Products
- Guidance Document: Fees for the Review of Drug Submissions and Applications
- Guidance for Industry: Product Monograph
- Guidance for Industry: Product Monograph Appendix I - Product Monograph Template - Schedule D

8. APPENDIX B: PMF GUIDANCE CROSS-REFERENCED TO COMMON TECHNICAL DOCUMENT MODULES

As a quick reference tool, all quality, non-clinical, and clinical Guidance sections are cross-referenced to suggested Common Technical Document (CTD) Modules in the table below. PMF-specific information in other CTD Modules than those suggested is acceptable.

Guidance section		CTD module		Up / down stream
2.3.	Quality information			
2.3.1.	Plant identification and description	3.2.S.2.3.	Control of Materials	up
2.3.2.	Expression systems	3.2.S.2.3.	Control of Materials	up
2.3.2.1.	Stable expression systems	3.2.S.2.3.	Control of Materials	up
2.3.2.2.	Transient expression systems	3.2.S.2.3. 3.2.S.2.6.	Control of Materials Manufacturing Process Development	up up
2.3.2.3.	Expression and genetic stability at the end of the growth phase	3.2.S.2.5.	Process Validation and/or Evaluation	up
2.3.3.	Generation of banking systems	3.2.S.2.3.	Control of Materials	up
2.3.4.	Upstream production phase (pre-harvest/harvest)	3.2.S.2.2. 3.2.S.2.3. 3.2.S.2.4. 3.2.S.2.5.	Description of Manufacturing Process and Process Controls Control of Materials Controls of Critical Steps and Intermediates Process Validation and/or Evaluation	up up up up
2.3.4.1.	Demonstration of quality system for adequate control	3.2.A.1. 3.2.A.1.	Facilities and Equipment Facilities and Equipment	up down
2.3.4.2.	Growing strategy	3.2.S.2.2. 3.2.S.2.4. 3.2.S.2.5.	Description of Manufacturing Process and Process Controls Controls of Critical Steps and Intermediates Process Validation and/or Evaluation	up up up
2.3.4.3.	Transfection (transient expression systems)	3.2.S.2.2.	Description of Manufacturing Process and Process Controls	up

Guidance section		CTD module		Up / down stream
	only)	3.2.S.2.2.	Description of Manufacturing Process and Process Controls	down
		3.2.S.2.3.	Control of Materials	up
		3.2.S.2.3.	Control of Materials	down
		3.2.S.3.2.	Impurities	up
		3.2.S.3.2.	Impurities	down
		3.2.S.2.5.	Process Validation and/or Evaluation	up
2.3.4.4.	Monitoring and safeguarding of plant health	3.2.S.2.2.	Description of Manufacturing Process and Process Controls	up
		3.2.S.2.4.	Controls of Critical Steps and Intermediates	up
2.3.4.5.	Harvesting (criteria for initiation of harvesting, controls for personnel, equipment, and facilities)	3.2.S.2.2.	Description of Manufacturing Process and Process Controls	up
		3.2.S.2.4.	Controls of Critical Steps and Intermediates	up
		3.2.S.2.5.	Process Validation and/or Evaluation	up
2.3.4.6.	Segregation strategy, cleaning, and change-over procedures	3.2.S.2.2.	Description of Manufacturing Process and Process Controls	up
		3.2.A.1.	Facilities and Equipment	up
2.3.4.7.	Container closure, conditions, and duration of storage of biological starting materials	3.2.S.2.2.	Description of Manufacturing Process and Process Controls	up
		3.2.S.2.5.	Process Validation and/or Evaluation	up
		3.2.S.6.	Container Closure System	up
		3.2.S.7.	Stability	up
2.3.5.	Downstream production phase (post-harvest)	3.2.S.2.6.	Manufacturing Process Development	down
2.3.5.1.	Material transport for processing	3.2.S.2.5.	Process Validation and/or Evaluation	up
		3.2.S.2.5.	Process Validation and/or Evaluation	down
2.3.5.2.	Batch definition	3.2.S.2.2.	Description of Manufacturing Process and Process Controls	up
		3.2.S.2.2.	Description of Manufacturing Process and Process Controls	down
2.3.5.3.	Purification process and in-process controls	3.2.S.2.2.	Description of Manufacturing Process and Process Controls	up
		3.2.S.2.2.	Description of Manufacturing Process and Process Controls	down
		3.2.S.2.3.	Control of Materials	up

Guidance section		CTD module		Up / down stream
		3.2.S.2.3.	Control of Materials	down
		3.2.S.2.4.	Controls of Critical Steps and Intermediates	up
		3.2.S.2.4.	Controls of Critical Steps and Intermediates	down
2.3.5.4.	Consistency of production	3.2.S.2.5.	Process Validation and/or Evaluation	up
		3.2.S.2.5.	Process Validation and/or Evaluation	down
		3.2.S.4.4.	Batch Analyses	up
		3.2.S.4.4.	Batch Analyses	down
2.3.6.	Impurities and potential for allergenicity	3.2.S.2.4.	Controls of Critical Steps and Intermediates	down
		3.2.S.3.2.	Impurities	down
		3.2.S.4.	Control of Drug Substance	down
2.3.6.1.	Potential product-related impurities	3.2.S.3.	Characterization	down
		3.2.S.3.2.	Impurities	down
		3.2.S.7.	Stability	down
2.3.6.2.	Potential process-related impurities	3.2.S.2.5.	Process Validation and/or Evaluation	down
		3.2.S.3.2.	Impurities	down
		3.2.S.4.1.	Specification	down
2.3.6.3.	Potential allergenicity of process/product-related impurities	3.2.S.2.5.	Process Validation and/or Evaluation	down
		3.2.S.3.2.	Impurities	down
		3.2.S.4.1.	Specification	down
2.3.6.4.	Risk management	3.2.S.3.2.	Impurities	down
2.3.7.	Manufacturing process development	3.2.S.2.6.	Manufacturing Process Development	up
2.3.8.	Release testing and specification limits	3.2.S.2.4.	Controls of Critical Steps and Intermediates	down
		3.2.S.4.1.	Specification	down
		3.2.S.4.5.	Justification of Specification	down
		3.2.P.4.1.	Specifications	
		3.2.P.5.6.	Justification of Specification(s)	
2.3.9.	Control of endogenous and adventitious contaminating agents	3.2.A.2.	Adventitious Agents Safety Evaluation	up
		3.2.A.2.	Adventitious Agents Safety Evaluation	down
2.4.	Non-clinical and clinical information			
2.4.1	Non-clinical	4.2.	Study Reports	
		4.2.3.	Toxicology	

Guidance section		CTD module		Up / down stream
		4.2.3.7.	Other Toxicity Studies (if available)	
2.4.1.1.	Toxicity	4.2.3.	Toxicology	
2.4.1.2.	Immunogenicity	4.2.3.7.	Other Toxicity Studies (if available)	
2.4.1.3.	Allergenicity	4.2.3.7.	Other Toxicity Studies (if available)	
2.4.2.	Clinical	5.	Clinical Study Reports	

9. APPENDIX C: COMMON TECHNICAL DOCUMENT MODULE 3 - UPSTREAM AND DOWNSTREAM

As a quick reference tool, sections in Common Technical Document (CTD) Module 3 suggested for both upstream (i.e., biological starting materials) and downstream (i.e., drug substance) processes are **highlighted in grey** in the table below. PMF-specific information in other CTD Modules than those suggested is acceptable.

CTD MODULE 3	
3	Quality
3.1	Table of Contents of Module 3
3.2	Body of Data
3.2.S	Drug Substance
3.2.S.1	General Information
3.2.S.1.1	Nomenclature
3.2.S.1.2	Structure
3.2.S.1.3	General Properties
3.2.S.2	Manufacture
3.2.S.2.1	Manufacturer(s)
3.2.S.2.2	Description of Manufacturing Process and Process Controls
3.2.S.2.3	Control of Materials
3.2.S.2.4	Controls of Critical Steps and Intermediates
3.2.S.2.5	Process Validation and/or Evaluation
3.2.S.2.6	Manufacturing Process Development
3.2.S.3	Characterization
3.2.S.3.1	Elucidation of Structure and other Characteristics
3.2.S.3.2	Impurities
3.2.S.4	Control of Drug Substance
3.2.S.4.1	Specification
3.2.S.4.2	Analytical Procedures
3.2.S.4.3	Validation of Analytical Procedures
3.2.S.4.4	Batch Analyses
3.2.S.4.5	Justification of Specification
3.2.S.5	Reference Standards or Materials
3.2.S.6	Container Closure System
3.2.S.7	Stability
3.2.P	Drug Product
3.2.P.1	Description and Composition of the Drug Product
3.2.P.2	Pharmaceutical Development
3.2.P.3	Manufacture
3.2.P.4	Control of Excipients
3.2.P.5	Control of Drug Product
3.2.P.6	Reference Standards or Materials
3.2.P.7	Container Closure System

CTD MODULE 3	
3.2.P.8	Stability
3.2.A	Appendices
3.2.A.1	Facilities and Equipment
3.2.A.2	Adventitious Agents Safety Evaluation
3.2.A.3	Excipients
3.2.R	Regional Information
3.2.R.1	Production Documentation
3.2.R.2	Medical Devices
3.2.R.3	Lot Release Documentation
3.2.R.4	Blood Establishment Data
3.3	Literature References