Health Canada Santé Canada

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

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Canada

Health Canada is responsible for helping Canadians maintain and improve their health. It ensures that high-quality health services are accessible, and works to reduce health risks.

Également disponible en français sous le titre : Ligne directrice à l'intention de l'industrie Préparation des données sur la qualité pour les présentations de drogues dans le format CTD : Produits biothérapeutiques et sanguins

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Document change log

General

- The three CTD Guidance documents applicable to Conventional Biotherapeutic Products, Biotechnological/biological (Biotech) products and Blood products have been merged. into one document as the three documents were sharing more than 95% of the content.
- The new title is ***Guidance for Industry - Preparation of the Quality Information for Drug Submissions in the CTD Format: Biotherapeutic and Blood Products*** (conventional biotherapeutic products are covered by the biotherapeutic product family).
- Module 2 and Module 3 referred to several outdated Health Canada guidance documents. References to guidance documents are updated to reflect current guidance documents.

Scope

The following products are excluded from the scope of this document:

- Vaccines for human use
- Gene and cell therapy products
- Cellular blood components
- Human plasma collected by plasmapheresis, and any relevant immunizing agents
- Radiopharmaceuticals, kits, and generators.

Vaccines have their own CTD guidance documents. Same for radiopharmaceuticals, kits, and generators. The CTD structure does not apply well to gene and cell therapy products, cellular blood components, human plasma collected by plasmapheresis, and immunizing agents.

Abbreviations and Acronyms:

A list of abbreviations and acronyms have now been inserted in the guidance document

CPID-B

- A completed copy of the CPID-B should be provided at the time of submission filing for an NDS under Module 1.3.6. Previously, the guidance document was stating that a CPID-B should be provided at the request of ORA, CBBB or CORR near the end of the review process and should be included in Module 1.4.1.
- Information on the batch size or scale, reprocessing and hold times has been added as new information to be provided under ***Description of Manufacturing Process and Process Controls.***
- Information on the Master Cell Bank and Working Cell Bank used in the manufacture of the drug substance has been added as new information to be provided under ***Control of Materials***.
- A section on the ***Reference Standards or Materials*** has been added under the drug substance and drug product sections.
- A section on the ***Container Closure System*** has been added under the drug substance section.
- A section on the ***Post-approval Stability Protocol and Stability Commitment*** has been added under the drug substance section.

- The anticipated range of commercial batch size has been added as new information to be provided under ***Drug Product, Batch Formula***.
- A summary of all facilities and equipment information has been added as new information to be provided under ***Appendices – Facilities and Equipment***.
- Information on all developmental or approved products (or alternatively the product types/classes) manufactured or manipulated in the same areas as the applicant has been expanded to include information on the *host cells or cell line* and should be provided under ***Appendices – Facilities and Equipment***.
- Once implemented, the ICH Q12 documents (i.e. Product Life Cycle Management Document which will contain the Establish Conditions and the associated reporting categories as well as the post-approval change management protocol(s)) should be included in Module 3.2.R.8 "Product Lifecycle Management Information".

Module 2 – Quality Overall Summary (QOS):

- A QOS-B blank template will be made available to the sponsor to avoid the filing of the QOS-CE with biological applications.
- The use of the Canadian QOS-B template will not be mandatory. Companies will be authorized to continue using global QOS template. However, the use of the Canadian QOS will reduce the number of clarification requests for missing information.
- The requirement to submit an annotated QOS in support of a post-approval change has been replaced with the requirement to submit an updated version of the QOS (appropriate version), with only the section(s) which have been revised or updated respective of the change(s), and maintain both the assigned CTD subsection numbering and the drug submission format.
- Clarification was made that an IMPD may be submitted in lieu of a QOS for CTAs and CTA-As to reflect the current practice.
- Clarification was made that Process validation and Method validation is not required for CTAs and CTA-As.
- Clarification was made that information on the Container Closure System used in the stability studies is required in the ***Stability section***.
- ***Facility information*** is no longer required for CTAs.
- ***Appendices:*** For approved products, a summary of facility information and cleaning procedure/validation has been added as new information to be provided in the QOS
- ***Regional information:*** A summary of the biosimilarity assessment provided under 3.2.R.5 should be provided in the QOS. Currently, this is not a requirement.

Module 3: Quality:

Drug substance:

- S.2.1: Additional information requested for testing site: "*For facility involved in testing, a description of whether the site is responsible to perform compendial and/or non-compendial testing should also be provided. If more than one testing site is proposed, the test(s) performed at each site should be listed*". A summary table has been proposed.

- S.2.3: The requirement to provide detailed information on Prepared Reagents has been deleted as it is not part of M4Q and we do not usually get this information in a submission.
- S.2.3: Clarification that Qualification Protocols used to generate Master Cell Banks and Working Cell Banks should be submitted.
- S.2.5: Clarification that the information provided in the validation report should support the current manufacturing process **and scale** proposed for commercial use (added "scale").
- S.3.2: Summary Tables have been proposed for reporting process-related and product-related impurities
- S.4.4: Clarification that the Certificates of Analysis no longer need to be provided.
- S.4.5: Justification of Specifications: Clarification that although the drug substance specification is only one part of the total control strategy, this section is appropriate to summarize the overall drug substance control strategy.
- S.5: Clarification that Qualification Protocols used for the qualification of future Reference Standards should be submitted.
- S.7: Stability: Clarification that the information on the stability batches and batch lineage should also be provided. This information may be reported using a proposed summary table.

Drug Product:

- P.2: Clarification that the summary and discussion of the risk assessment for nitrosamine impurities in the drug product should be provided in this section.
- P.2.6: Added that: Compatibility studies should be conducted for the proposed commercial drug product using closed system transfer devices (e.g., with intravenous administration sets) and should include extractable and leachable studies with the dosage devices. Compatibility study design including dose preparation and administration components, type of materials, stress conditions, hold times, temperatures, stability indicating tests and results should also be provided.
- P.3.1: Need now to identify the importer and distributor. Additional information requested for testing site as for the drug substance: "*For facility involved in testing, a description of whether the site is responsible to perform compendial and/or non-compendial testing should also be provided. If more than one testing site is proposed, the test(s) performed at each site should be listed*". A summary table has been proposed.
- P.3.2: Clarification that the anticipated range of commercial batch size should be based on the available manufacturing experience.
- P.5.3 : Validation of analytical procedures: Clarification was made that for analytical methods used at release or stability that have been transferred during development, information demonstrating technical transfer qualification for the non-pharmacopoeial assays should be provided.
- P.5.4: Batch analysis: Clarification that in the description of the batch analysis, this description should include the batch number, production scale, date of manufacture, production site, manufacturing process and use. Confirmation should be provided that the batch analysis data results reported in the submission were generated by the company responsible for routine testing of the drug product.

- P.5.4. Batch Analysis: Clarification that the Certificates of Analysis no longer need to be provided.
- P.5.5: Characterization of impurities: Clarification that the impurity limits (including degradation products arising from manufacturing, storage, or detected in stability study batches) should be set taking into account the totality of what will be administered to the patient (i.e. in combination with other drugs, diluent or IV infusion solution).
- P.5.6: Justification of Specifications (same as for Drug Substance): Clarification that although the drug product specification is only one part of the total control strategy, this section is appropriate to summarize the overall drug product control strategy.
- P.6: Clarification that Qualification Protocols used for the qualification of future Reference Standards should be submitted.
- P.7: Clarification that information on the neck opening size for vials should be provided as part of the Container Closure System information.
- P.8: Stability: Clarification that information on the stability batches and batch lineage should also be provided. This information may be reported using a proposed summary table.
- A.1: Clarification that a summary of the environmental monitoring program, including data from the last 12 months in classified areas, should be provided.
- A.2: Clarification that viral reduction studies should be performed using both new and used resins.
- A.2: Clarification that the detailed safety factor calculation should be performed based on a worst-case scenario.
- R.1: Executed Batch Records: Clarification that Executed batch records are no longer required at time of filing to support a marketing application (NDS or DIN-B) or any post-NOC changes (S/NDS, NC or DIN-B). However, these may be requested during review and should be available within 15 days upon request. If requested, the documentation submitted for the executed batches should be for products manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. Any notations made by operators on the executed production documents should be clearly legible.
- R.2: Medical devices: Clarification has been provided on the classification of combination products with a medical device.
- R.4: New section added for “Yearly Biologic Product Report”.
- R.5: New section added for “Assessment of Similarity”.
- R.6: New section added for “On Site Evaluation”.
- R.7: New section added for “Other Regional Information”.
- R.8: New section added for “Product Lifecycle Management Information”.

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.

Table of Contents

1. Introduction

1.1 Purpose

This document is intended to provide additional guidance to industry, for the preparation of the quality information for Drug Submissions, structured using the International Conference on Harmonisation (ICH) Common Technical Document (CTD) format. This document supplements the Health Canada Guidance documents for Industry on the preparation of various types of drug submissions in the CTD format. In addition, this document references other available domestic Quality guidance documents that can be useful in preparing the technical or scientific information required for certain sections of the submission.

For additional guidance in preparing the drug submission, applicants should consult the Office of Regulatory Affairs (ORA) within the Biologic and Radiopharmaceutical Drugs Directorate (BRDD). The applicant is also advised to consult the canada.ca website (https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies.html) for the latest information (e.g. Notices).

1.2 Scope

This guidance document applies to all biologically active protein products that are used in the treatment of human diseases (e.g., Biotherapeutic products, Conventional Biotherapeutic products and Blood products) and those intentionally modified by, for example, fusion proteins, PEGylation, conjugation with a cytotoxic drug, or modification of rDNA sequences.

Biotherapeutic products include any biotechnological/ biological proteins and polypeptides, their derivatives, and products of which they are components (e.g. conjugates), that are produced from recombinant or non-recombinant cell-culture expression systems and which can be highly purified and characterized using an appropriate array of analytical procedures. These guidelines also apply to protein products used for in vivo diagnosis (e.g. monoclonal antibody products used for imaging).

Conventional Biotherapeutic products include any biological drugs isolated from biological sources such as tissues, organs and body fluids. For example, this would include those Schedule D drugs (of the Canadian Food and Drugs Act and Regulations) such as anterior pituitary extracts, snake venom, and allergenic substances.

Blood products include any human or animal blood, plasma, and serum-derived proteins or products, including immune proteins such as immunoglobulins, antibodies, coagulation proteins, which can be purified by fractionation and other viral inactivation or removal steps, and characterized using an appropriate array of analytical procedures. For example, this would include those Schedule D drugs (of the Canadian Food and Drugs Act and

Regulations) listed as blood and blood derivatives.

These guidelines do not cover vaccines for human use, gene and cell therapy products, cellular blood components, human plasma collected by plasmapheresis, radiopharmaceuticals, kits, and generators, and any relevant immunizing agents. Detailed and specific guidelines for vaccines for human use are available in the Health Canada Guidance Document entitled *Harmonized Requirements for the Licensing of Vaccines and Guidelines for the Preparation of an Application* (https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/drug/harmonized-requirements-licensing-vaccines-guidelines-preparation-application.html). Detailed and specific guidelines for radiopharmaceuticals, kits, and generators are available in the Health Canada Guidance Document entitled *Radiopharmaceuticals, Kits, and Generators: Submission Information for Schedule C Drugs* (https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/drug/radiopharmaceuticals-schedule-c.html).

1.3 Abbreviations and Acronyms

BAN	British Approved Name
BRDD	Biologic and Radiopharmaceutical Drugs Directorate
CAS	Chemical Abstracts Service
CBBB	Centre for Blood, Blood Products and Biotherapeutics
CE	Chemical Entities
CoA	Certificate of Analysis
CORR	Centre for Oncology, Radiopharmaceuticals and Research
CPID	Certified Product Information Document
CPID-B	Certified Product Information Document - Biologics
CTA	Clinical Trial Application
CTA-A	Clinical Trial Application-Amendments
CTD	Common Technical Document
CTD-E	Common Technical Document-Efficacy
CTD-S	Common Technical Document-Safety
DIN-B	Biological Drug Identification Number Application
DNA	Deoxyribonucleic acid
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPC	In process controls
ISO	International Organization for Standardization
INN	International Nonproprietary Name
JAN	Japanese Accepted Name
MF	Master File

MRA	Mutual Recognition Agreement
MS	Microsoft® Word
NAS	New Active Substance
NC	Notifiable Change
NDS	New Drug Submission
NOAEL	No-observed-adverse-effect-level
NOC	Notice of Compliance
ORA	Office of Regulatory Affairs
OSE	On-Site Evaluation
PDE	Permitted Daily Exposure
PEG	Polyethylene glycol
QIS-R	Quality Information Summary - Radiopharmaceuticals
QOS	Quality Overall Summary
QOS-B	Quality Overall Summary – Biologics (Schedule D drugs)
rDNA	recombinant DNA
SMF	Site Master File
SNDS	Supplemental New Drug Submission
SOP	Standard Operating Procedure
USAN	United States Adopted Name
YBPR	Yearly Biologic Product Report

2. Location, format and content of the quality information

The applicant should follow the referenced ICH and domestic guidance documents in preparing and filing the Quality information under Module 1.3.6, Module 2.3, and Module 3 for a drug submission in the CTD format and for submitting any other necessary Quality-related information during the review process.

2.1 Module 1.3.6: Certified Product Information Document(CPID)

2.1.1 Purpose of the CPID-B

The CPID-B is a condensed summary of current and specific quality information attested by the manufacturer and/or sponsor and it serves as a concise summary of critical quality information that the BRDD retains on file for reference.

2.1.2 Selection of a CPID-B Template

The **Certified Product Information Document – Biologics (CPID-B (Schedule D drugs)) template** (or the appropriate parts of it) should be used with a drug submission in the CTD format for any biological product (described under Schedule D of the Canadian Food and Drugs Act and Regulations), or any combination drug for human use, which has a biological component. For example, the CPID-B (Schedule D drugs) template should be used for a Biotech product, a plasma-derived blood product or a natural therapeutic product.

The CPID-B template is available:

- CPID-B template

2.1.3 Preparation of the CPID-B (Schedule D drugs)

To ease the preparation of the CPID-B (Schedule D drugs), the applicant is encouraged to follow in particular, the guidance provided on the Supporting Quality Information (provided under 2.3.5 of this guidance document) on the preparation of summarized information or tabulated summaries, and which is easily identified by, "[Copy information to CPID-B (Schedule D drugs) under a certain section]".

In addition, the applicant is encouraged to subsequently follow the guidance provided on the CPID-B (Schedule D drugs) (provided under 2.1.5) for instructions on how to prepare it [see text within square brackets]. This guidance identifies the information from Module 3, once it has been completed, that can be conveniently "copied and pasted" into the corresponding section of the CPID-B (Schedule D drugs) template. The most current information, including any updated or revised information during the review process, should be used to prepare the CPID-B (Schedule D drugs). The applicant should also provide the information described under the INTRODUCTION section of the CPID-B (Schedule D drugs).

2.1.4 Submission of the CPID-B (Schedule D drugs)

For a New Drug Submission (NDS) or a Biological Drug Identification Number Application (DIN-B), a clean copy of the CPID-B should be provided at the time of submission filing under Module 1.3.6. The clean version should contain information from Module 3 and should not contain any cross-referencing and hyperlinks, except for the Product Lifecycle Management Document.

With the filing of Supplemental New Drug Submissions (SNDSs), Notifiable Changes (NCs), Amendment to a DIN-B or a Yearly Biologic Product Report (YBPR), the CPID-B may require updating, as necessary, in order to reflect information relevant to the change(s).

With these types of submissions, a completed annotated and clean copy of the CPID-B should be provided at the time of submission filing under Module 1.3.6. The text of the annotated copy at the time of filing should reflect all changes that have been made, including Level III and Level IV changes, as appropriate. The clean version should not contain any cross-referencing and hyperlinks, except for the Product Lifecycle Management Document.

With the filing of a Clinical Trial Application (CTA) or a Clinical Trial Application-Amendment (CTA-A), a completed CPID-B is not required.

References:

Health Canada Guidance Documents

Filing submissions electronically (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/filing-submissions-electronically.html) landing page, if applicable and as applicable:

- Organisation and Document Placement for Canadian Module 1 (available upon request)
- Preparation of Regulatory Activities in the Electronic Common Technical Document (eCTD) Format (available upon request)
- Guidance Document - Preparation of Regulatory Activities in Non-eCTD Format (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/common-technical-document/updated-guidance-document-preparation-regulatory-activities-non-ectd-electronic-only-format.html)

Health Canada Templates:

- Certified Product Information Document - Biologics (CPID-B (Schedule D drugs)) (https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/preparation-quality-information-drug-submissions-ctd-format-biotherapeutic-blood-products/certified-product-information-document-biologics-schedule-d-drugs.html)

ICH Guidelines:

- M4Q
- Q13 (CM)

2.1.5 Guidance on the CPID-B (Schedule D drugs)

Start of "Module 1.3.6 CPID-B (Schedule D drugs) Guidance"

INTRODUCTION

Submission File#

NDS Approval Date and Control#:

CPID-B Revision Date and Control#:

Proprietary Name:

Non-proprietary name or common name of the drug substance:

Company Name:

Name of Canadian Distributor:

Therapeutic or Pharmacological Classification:

Dosage form(s): e.g., liquid, lyophilized powder

Presentation(s): e.g., pre-filled syringes, vials, autoinjector, cartridges

Strength(s) or Concentration(s):

Fill volume(s):

Route(s) of Administration:

Maximum Daily Dose: (The dose should be specified and should be based on the dosing instructions in the Product Monograph)

New Active Substance (NAS)?

S DRUG SUBSTANCE (COMMON NAME, MANUFACTURER)

Manufacture (common name, manufacturer)

Manufacturer(s) (common name, manufacturer)

Information on the manufacturer(s): [Insert the completed Module 3.2.S.2.1.]

Description of Manufacturing Process and Process Controls (common name, manufacturer)

A flow diagram of the manufacturing process and process controls: [Insert the flow diagram(s), from the completed Module *3.2.S.2.2*.], including information on the cell line (e.g., CHO, *E.coli*, etc.).

Information on the batch size or scale [Insert the information from the completed Module *3.2.S.2.2*.]

Information on reprocessing [Insert the information from the completed Module *3.2.S.2.2*.]

Information on hold times [Insert the information from the completed Module *3.2.S.2.2*.]

Control of Materials (common name, manufacturer)

A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the drug substance, including the Master Cell Bank(s) (MCBs) and Working Cell Bank(s) (WCBs) used, i.e., batch number of the cell bank, in the manufacture of the drug substance: [Insert the tabulated summary of the biological raw material(s) used, from the completed Module *3.2.S.2.3*.]

Controls of Critical Steps and Intermediates (common name, manufacturer)

A summary of critical manufacturing steps, process controls performed, and acceptance criteria: [Insert a summary of critical manufacturing steps, process controls performed, and acceptance criteria from the completed Module *3.2.S.2.4*, under *Critical Steps*.]

Highlight critical process intermediates, their quality and control: [Insert a summary of the quality, control and storage conditions of intermediates isolated during the process from the completed Module *3.2.S.2.4*, under *Intermediates*.]

Characterisation (common name, manufacturer)

Elucidation of Structure and other Characteristics (common name, manufacturer)

A description of the desired product and product-related substances and a summary of general properties, characteristic features and characterisation data (for example, primary and higher order structure and biological activity): [Insert a summarized description of this information from the completed Module *3.2.S.3.1*.]

Impurities (common name, manufacturer)

A tabulated summary of the impurities data: [Insert the tabulated summary on actual impurity levels detected from the completed Module *3.2.S.3.2*.]

Control of Drug Substance (common name, manufacturer)

Specification (common name, manufacturer)

Specification for the drug substance: [Insert the specification for the drug substance from the completed Module *3.2.S.4.1*.]

The Drug Substance standard declared by the company responsible for routine testing: [Insert the declared drug substance standard from the completed Module *3.2.S.4.1*.]

Reference Standards or Materials (common name, manufacturer)

Information on the reference standards or reference materials used for testing of the drug substance: [Insert a brief summary of the information, including the name(s) and use(s) of the reference standards or reference materials from the completed Module *3.2.S.5.*]

Container Closure System (common name, dosage form)

A brief description of the container closure system for the drug substance: [Insert a brief description of the container closure system for the drug substance from the completed Module *3.2.S.6.*]

Stability (common name, manufacturer)

Stability Summary and Conclusions (common name, manufacturer)

The proposed storage conditions and shelf-life: [Insert the proposed storage conditions and shelf-life, where relevant from the completed Module *3.2.S.7.1*.]

Post-approval Stability Protocol and Stability Commitment (common name, manufacturer)

The drug substance post-approval stability protocol and annual stability commitment: [Insert the post-approval stability protocol for annual testing from the completed Module 3.2.S.7.2]

P DRUG PRODUCT (PROPRIETARY NAME, DOSAGE FORM)

Manufacture (proprietary name, dosage form)

Manufacturer(s) (proprietary name, dosage form)

Information on the manufacturer(s): [Insert the completed Module *3.2.P.3.1*.]

Batch Formula (proprietary name, dosage form)

Information on the batch formula and the anticipated range of commercial (production) batch sizes: [Insert the tabulated summary on the batch formula and batch size range from the completed Module *3.2.P.3.2*.]

Description of Manufacturing Process and Process Controls (proprietary name, dosage form)

A flow diagram of the manufacturing process and process controls: [Insert the process flow diagram from the completed Module *3.2.P.3.3*.]

Information on reprocessing [Insert the information from the completed Module *3.2.P.3.3*.]

Controls of Critical Steps and Intermediates (proprietary name, dosage form)

A summary of critical manufacturing steps, process controls performed, and acceptance criteria: [Insert a summary of critical manufacturing steps, process controls performed, and acceptance criteria from the completed Module *3.2.P.3.4*, under *Critical Steps*.]

Highlight critical process intermediates, their quality and control: [Insert information on the quality and control of intermediates isolated during the process, from the completed Module *3.2.P.3.4*, under *Intermediates*.]

Control of Excipients (proprietary name, dosage form)

Excipients of Human or Animal Origin (proprietary name, dosage form)

A summary of excipients of human or animal origin that are used: [Insert the tabulated summary of excipients of human or animal origin that are used from the completed Module *3.2.P.4.5*.]

(†) A confirmation, that none of the non-medicinal ingredients (excipients) which appear in the final product are prohibited for use in drugs by the Canadian Food and Drugs Act and Regulations, should be provided.

Control of Drug Product (proprietary name, dosage form)

Specification(s) (proprietary name, dosage form)

Specification(s) for the drug product: [Insert the specification(s) for the drug product from the completed Module *3.2.P.5.1*.]

The Drug Product standard declared by the company responsible for routine release testing and post-market stability testing: [Insert the declared drug product release standard from the completed Module *3.2.P.5.1*.]

Reference Standards or Materials (proprietary name, manufacturer)

Information on the reference standards or reference materials used for testing of the drug product if not previously provided in S DRUG SUBSTANCE: Reference Standards or Materials [Insert a brief summary of the information, including the name(s) and use(s) of the reference standards or reference materials from the completed Module *3.2.P.6.]*

Container Closure System (proprietary name, dosage form)

A brief description of the container closure system for the drug product: [Insert a brief description of the container closure system for the drug product from the completed Module 3.2.P.7.]

Stability (proprietary name, dosage form)

Stability Summary and Conclusion (proprietary name, dosage form)

The proposed labelled storage conditions and shelf-life, including after reconstitution and in-use storage conditions (if applicable): [Insert the proposed labelled storage conditions and shelf-life, including after reconstitution and in-use storage conditions (if applicable) from the completed Module *3.2.P.8.1*.]

Post-approval Stability Protocol and Stability Commitment (proprietary name, dosage form)

The post-approval stability protocol and annual stability commitment: [Insert the post-approval stability protocol and annual stability commitment from the completed Module *3.2.P.8.2*.]

A APPENDICES

Facilities and Equipment (common/proprietary name, manufacturer)

A summary of all manufacturing facilities (e.g., name, single- or multi-product facility) and relevant product-contact equipment information: [Insert the summarized information of all facilities and equipment from the completed Module *3.2.A.1.*]

Information on all developmental or approved products (or alternatively the product types/classes) manufactured or manipulated in the same areas as the applicant's product, along with the cell line/expression system used (e.g., *E.coli*, CHO) or source material (if applicable), including change over procedures if upstream processing is occurring in the facility: [Insert information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product from the completed Module *3.2.A.1.*]

Adventitious Agents Safety Evaluation (common name, dosage form, manufacturer)

A tabulated summary of the reduction factors for viral clearance: [Insert the tabulated summary of the reduction factors for viral clearance from the completed Module *3.2.A.2*, under *Viral Clearance Studies*.]

The calculation of estimated particles / dose, where relevant. The calculation should also be expressed as "one retroviral-like particle per number of doses": [Insert the calculation of estimated particles/ dose, where relevant from the completed Module *3.2.A.2*, under *Viral Clearance Studies*.]

R REGIONAL INFORMATION

Medical Devices (proprietary name, dosage form)

A summary of the information on novel medical devices: [Insert a summary of the information on any novel medical devices used to deliver the dosage form that are external to the drug product (e.g. inhalation devices) from Module 3.2.R.2, under *Medical Devices*.]

Product Lifecycle Management Information (proprietary name, dosage form, manufacturer)

[Insert a reference (hyperlink) to the Product Lifecycle Management Document (PLCM) located in Module 3.2.R.8, under *Product Lifecycle Management Information*.]

End of "Module 1.3.6 CPID-B (Schedule D drugs) Guidance"

2.2 Module 2.3: Quality Overall Summary (QOS)

2.2.1 Purpose of the QOS-B (Schedule D drugs)

The Quality Overall Summary – Biologics (QOS-B (Schedule D drugs)) template, once filled in, provides an overview of the Quality information intended to support the approval of the drug submission.

As described in the Health Canada guidance documents Preparation of Regulatory Activities in the Electronic Common Technical Document (eCTD) Format (available upon request) and Guidance Document - Preparation of Regulatory Activities in Non-eCTD Format (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/common-technical-document/updated-guidance-document-preparation-regulatory-activities-non-ectd-electronic-only-format.html), the QOS should be provided in both PDF and Microsoft® Word format.

2.2.2 Preparation of the QOS-B (Schedule D drugs)

The ICH Harmonised Tripartite Guidelines *M4Q* (https://database.ich.org/sites/default/files/M4Q_R1_Guideline.pdf) and the *Common Technical Document-Quality Questions and Answers/ Location Issues document* (https://database.ich.org/sites/default/files/M4Q_Q%26As_R1_Q%26As.pdf) and the current guidance document on the QOS (provided under *2.2.4*), should be referred to for preparing the summarized Quality information required under Module 2.3.

In particular cases, such as with combination products, it may be necessary to refer to more than one product-specific guidance for the preparation of the QOS or a part of it (as the case may be). As an example, for a radiolabeled monoclonal antibody, Modules 2.3.S, (2.3.P) and 2.3.A should be prepared following the QOS-B guidance for the monoclonal antibody part, and Modules (2.3.S), 2.3.P, and 2.3.A following the Quality Information Summary - Radiopharmaceuticals (QIS-R) guidance for the radiopharmaceutical part, and submitted under Module 2.3.

Within this guidance on the QOS-B, the ICH guideline on preparing the QOS has been

reproduced, streamlined (i.e. it excludes the ICH guideline for NCE products), and integrated with the Health Canada guidance, with some added clarifications and the identification of regional information for Canada.

To ease the preparation of the QOS-B, the applicant is encouraged to use the blank Health Canada template for the QOS-B and to follow the Health Canada Guidance on the Supporting Quality Information (provided under *2.3.5*) for the preparation of summarized information or tabulated summaries, which is easily identified by, "[Copy information to QOS under a specified section]".

If the drug submission describes for example, more than one drug substance, manufacturer, dosage form, formulation, type of packaging, and/or strength, the applicant should summarize this information in the QOS-B using a similar format as in Module 3.2 BODY OF DATA. For more guidance, see section *2.3.2* of this guidance document. In addition, the applicant is encouraged to subsequently follow the text within [square brackets] of the Guidance on the QOS-B (provided under *2.2.4*), which identifies the information from Module 3, that can be conveniently "copied and pasted" into the corresponding section of the QOS, once it has been completed.

For definitions of a document within the QOS, refer to the *M4Q: Common Technical Document-Quality Questions and Answers/ Location Issues document* (https://database.ich.org/sites/default/files/M4Q_Q%26As_R1_Q%26As.pdf).

Rather than duplicating information within the submission, should a cross-reference need to be made in the QOS-B to supporting or related information which is contained in any Modules or subsections, besides Module 3, the cross-reference should be sufficiently detailed, so as to allow the appropriate information to be easily located within the submission.

2.2.3 Submission of the QOS-B (Schedule D drugs)

For New Drug Submissions (NDS), the applicant should submit a completed QOS-B in its entirety.

For Supplemental New Drug Submissions (SNDSs) with changes to the Quality information, the applicant should submit an updated version of the QOS-B (appropriate version), with only the section(s) which have been revised or updated respective of the change(s), and maintain both the assigned CTD subsection numbering and the drug submission format. A document clearly detailing the proposed changes should be submitted.

For Notifiable Changes (NCs) related to the Quality information, the completion of a QOS-B is unnecessary. However, a document clearly detailing the proposed changes should be submitted.

For a Biological DIN Application (DIN-B), the applicant should submit a completed QOS-B in its entirety (for DIN-B equivalent to NDS). For DIN-B equivalent to SNDS, the applicant should submit an updated version of the QOS-B (appropriate version), with only the section(s) which have been revised or updated respective of the change(s), and maintain both the assigned CTD subsection numbering and the drug submission format. For DIN-B equivalent to NC, the completion of a QOS-B is unnecessary. However, a document clearly detailing the proposed changes should be submitted.

For the initial filing of a Clinical Trial Application (CTA), the applicant should submit a completed QOS-B with, as a minimum, those subsections or parts which have an asterisk (*) beside the guidance or heading. Note that these guidance documents were not written specifically for CTAs and may not necessarily apply to the same extent. It is understood that depending on the stage of drug development, a limited amount of information may be available for a CTA; in which case, the sponsor should provide whatever data are available at that time.

With subsequent CTA filings for the same drug (e.g. Phase 2 or 3 studies), with changes to the quality information, the applicant should submit an updated version of the QOS-B (appropriate version), with only the section(s) which have been revised or updated respective of the change(s), and maintain both the assigned CTD subsection numbering and the drug submission format. A document clearly detailing the proposed changes should also be submitted. Sponsors may complete and submit other subsections of the QOS-B which exclude an asterisk, as that information becomes available during the course of drug development (e.g. Phase 2 and 3 CTAs), or as advance preparation of an NDS.

If a particular section contains a significant amount of information, the applicant should place it in Module 3 and cross-reference to it. Cross-referencing is permitted when the Phase 3 quality information is the same as the Phase 2 quality information.

Alternatively, for CTAs, the quality information may be provided as part of an Investigational Medicinal Product Dossier (IMPD) in lieu of a QOS-B. Additional acceptable structures below apply when the IMPD is provided in lieu of QOS-B. The QOS Introduction is required when providing an IMPD.

For a Clinical Trial Application-Amendment (CTA-A), with changes to the quality information, the applicant should submit an updated version of the QOS-B (appropriate version), with only the section(s) which have been revised or updated respective of the change(s), and maintain both the assigned CTD subsection numbering and the drug submission format. A document clearly detailing the proposed changes should also be submitted. Sponsors may complete and submit other subsections of the QOS-B which exclude an asterisk, as that information becomes available during the course of drug development (e.g. Phase 2 and 3 CTAs), or as advance preparation of an NDS.

The applicant should consult with the ORA for additional guidance on the technical data requirements for their particular drug submission, if necessary. As for CTAs, a revised IMPD may be filed in lieu of a revised QOS in CTA-As.

The completed QOS-B should be submitted as part of Module 2.3, including for a CTA or CTA-A. The applicant should refer to the Health Canada Guidance documents for Industry on the preparation of various types of drug submissions in the CTD format and the ICH Guideline, *The Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality – M4Q*, for further guidance on document pagination and segregation, section numbering within documents, and table of contents formatting.

References:

ICH Guidelines:

- M4Q
- M4Q Quality & Answers / Location Issues

Health Canada Guidance Documents:

- Organisation and Document Placement for Canadian Module 1 (available upon request)
- Clinical Trial Applications in eCTD format (available upon request)
- Guidance Document - Preparation of Regulatory Activities in Non-eCTD Format (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/common-technical-document/updated-guidance-document-preparation-regulatory-activities-non-ectd-electronic-only-format.html)

2.2.4 Guidance on the QOS-B (Schedule D drugs)

The Quality Overall Summary – Biologics (QOS-B) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD.

(*) The QOS should include sufficient information from each section to provide the Quality reviewer with an overview of Module 3. The QOS should also emphasize critical key parameters of the product and provide, for instance, justification in cases where guidance documents were not followed. The QOS should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies discussed under the CTD-S module), including cross-referencing to volume and page number in other Modules, if applicable.

(*) Module 2.3 QOS-B normally should not exceed 80 pages of text, excluding tables and figures.

The *italicised* text below indicates where tables, figures, or other items can be imported directly from Module 3. Following the guidance provided under 2.3.5 of this document on the supporting quality information, if Module 3 is properly completed, essentially all of the information suggested for the QOS, whether in italics or not, can be imported directly from Module 3, except for the information under Introduction.

Start of "Module 2.3 QOS-B Guidance"

INTRODUCTION

The introduction should include (*) proprietary name, (*) non-proprietary name or common name of the drug substance, (*) company name, (*) dosage form(s), (*) strength(s), (*) route of administration, and proposed indication(s).

2.3.S DRUG SUBSTANCE (COMMON NAME, MANUFACTURER)

2.3.S.1 General Information (common name, manufacturer)

(*) Information from 3.2.S.1 should be included. [Insert the information from the completed Module 3.2.S.1 as follows: The nomenclature of the drug substance from *3.2.S.1.1*; Information on the structure of the drug substance from *3.2.S.1.2*; and a list of the physicochemical and other relevant properties of the drug substance from *3.2.S.1.3*.]

2.3.S.2 Manufacture (common name, manufacturer)

Information from 3.2.S.2 should be included:

(*) Information on the manufacturer(s); [The name, address, and responsibility of each manufacturer, including contractors and each proposed production site or facility involved in manufacturing and testing should be provided in a tabulated summary. Insert the completed Module *3.2.S.2.1*.]

- (*) A brief description of the manufacturing process (including, for example, reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality.

For Conventional Biotherapeutic products:
[Insert the information from the completed Module *3.2.S.2.2* as follows: The explanation of the batch numbering system, information regarding any pooling of intermediates, and information on the batch size or scale, from under **Batch(es) and scale definition**; The description of the manufacturing process, controls, reprocessing procedures, and any transfer of materials, from under **Extraction, Purification, modification reactions and formulation (when applicable)**, **Filling, storage and transportation (shipping)** in this order; Information on the container closure system,

storage, and shipping condition of the drug substance, from under **Filling, storage and transportation (shipping).**]

For Biotherapeutic products:
[Insert the information from the completed Module *3.2.S.2.2* as follows: The explanation of the batch numbering system, information regarding any pooling of intermediates, and information on the batch size or scale, from under **Cell culture and harvest, Purification, modification reactions and formulation (when applicable)**, **Filling, storage and transportation (shipping)** in this order; Information on the container closure system, storage, and shipping condition of the drug substance, from under **Filling, storage and transportation (shipping).**]

For Blood products:
[Insert the information from the completed Module *3.2.S.2.2* as follows: The explanation of the batch numbering system, information regarding any pooling of intermediates, and information on the batch size or scale, from under **Fractionation and/or Purification**, **Filling, storage and transportation (shipping) for blood products** in this order; Information on the container closure system, storage and shipping conditions of the drug substance, from under **Filling, storage and transportation (shipping)**.]

- (*) *A flow diagram, as provided in 3.2.S.2.2;*

  For Conventional Biotherapeutic products:
  [Insert either the overall process flow diagram or the flow diagrams under **Extraction, Purification, modification reactions and formulation (when applicable)**, in this order from the completed Module *3.2.S.2.2*.]

  For Biotherapeutic products:
  [Insert either the overall process flow diagram or the flow diagrams under **Cell culture and harvest, Purification, modification reactions and formulation (when applicable)**, in this order from the completed Module *3.2.S.2.2*.]

  For Blood products:
  [Insert either the overall process flow diagram or the flow diagrams under **Fractionation and/or Purification**, in this order from the completed Module *3.2.S.2.2*.]

- (*) A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the drug substance as described in *3.2.S.2.3*;

  For Conventional Biotherapeutic products:
  [Insert the information from the completed Module *3.2.S.2.3* as follows: The summary (e.g. tabulated summary) of the biological raw material(s) used, from under **Control of Source and Starting Materials of Biological Origin**; Information on the

control of starting material from under **Control of Starting Material for the Conventional Biotherapeutic**]

For Biotherapeutic products:
[Insert the information from the completed Module *3.2.S.2.3* as follows: The summary (e.g. tabulated summary) of the biological raw material(s) used, from under **Control of Source and Starting Materials of Biological Origin**; Information on the source of the cell substrate and analysis of the expression construct, from under **Source, history, and generation of the cell substrate**; Information on the cell banking system, quality control activities, and cell line stability from under **Cell banking system, characterisation, and testing.**]

For Blood products:
[Insert the information from the completed Module *3.2.S.2.3* as follows: The summary (e.g. tabulated summary) of the biological raw material(s) used, from under **Control of Source and Starting Materials of Biological Origin**; Information on the origin and collection of the plasma from under **Origin and Collection of the Source and Starting Material**; Information on the quality control activities and safety measures taken on the source and starting material from under **Donor Suitability, Testing and Screening, and Additional Safety Measures on the Source and/or Starting Material.**]

- List the critical manufacturing steps, process controls, and acceptance criteria. [Insert the information from the completed Module *3.2.S.2.4*]

- (*) Highlight critical process intermediates, as described in *3.2.S.2.4*; [Insert a summary of the quality, control and storage conditions of intermediates isolated during the process from the completed Module *3.2.S.2.4*.]

- A description of process validation and/or evaluation, as described in *3.2.S.2.5*. [Insert a summary of the process validation and/or evaluation studies from the completed Module *3.2.S.2.5*.]

- (*) A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in *3.2.S.2.6*. The QOS should also cross-reference the non-clinical and clinical studies that used batches affected by these manufacturing changes, as provided in the CTD-S and CTD-E modules of the dossier, if applicable. [Insert the information from the completed Module *3.2.S.2.6* as follows: A brief summary of major manufacturing changes made through development and conclusions from the assessment used to evaluate product consistency; A cross-reference to the location of nonclinical and clinical studies provided in other modules of the submission, in which drug substance batches that were affected by a significant manufacturing change had been used.]

2.3.S.3 Characterisation (common name, manufacturer)

(*) A description of the desired product and product-related substances and a summary of general properties, characteristic features and characterisation data (for example, primary, secondary, tertiary and/or higher order structure and biological activity), as described in *3.2.S.3.1*, should be included. [Insert a summarized description of this information from the completed Module *3.2.S.3.1*.]

(*) The QOS should summarise the data on potential and actual impurities arising from the manufacture and/or degradation, including the control strategy for each impurity. It should also summarise the basis for setting the acceptance criteria for individual and total impurities, based on supporting evidence where applicable (e.g., toxicological limits, NOAEL, PDE, etc.).

The QOS should also summarise the impurity levels in batches of the drug substance used in the non-clinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process.

(*) If filing a CTA/CTA-A, the QOS should also summarise the impurity levels in batches of the drug substance produced to-date and used both in the non-clinical studies and/or in the clinical trials, if available. These results, and a discussion of the proposed limits, should be discussed.

(*) *A tabulated summary of the data provided in 3.2.S.3.2, with graphical representation, where appropriate should be included.* [Insert the tabulated summary on actual impurity levels detected from the completed Module *3.2.S.3.2*.]

The QOS should state how the proposed impurity limits are qualified. [Insert the discussion of results, which are close to or outside limits, and the rationale for the choice of tests, the proposed limits and their qualification from the completed Module *3.2.S.3.2*.]

2.3.S.4 Control of Drug Substance (common name, manufacturer)

(*) A brief summary of the justification of the specification(s), (*) of the analytical procedures, and of the validation of the analytical procedures, should be included. [Insert the information from the completed Module 3.2.S.4 as follows: A summary of the analytical procedures from *3.2.S.4.2*; A summary of the validation of analytical procedures from *3.2.S.4.3*; and a summary of the justification of the specification from section 3*.2.S.4.5*.]

(*) *Specification from 3.2.S.4.1 should be provided.* [Insert the specification for the drug substance from the completed Module *3.2.S.4.1*.]

(*) The drug substance standard declared by the company responsible for routine release testing should be specified. [Insert the declared drug substance standard from the completed Module *3.2.S.4.1*.]

(*) *A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.* [Insert the written summary of the batch analyses, the tabulated summary (or graphical representation where appropriate) of results (other than impurities) from in vivo study batches and recent production batches from the completed Module *3.2.S.4.4*.] If filing a CTA/CTA-A, submit all available information, on all batches produced to-date and for which complete manufacturing documentation has been provided.

2.3.S.5 Reference Standards or Materials (common name, manufacturer)

(*) Information from *3.2.S.5* (tabulated presentation, where appropriate including name(s) and use(s)) should be included. [Insert information on the reference standards or reference materials used for testing of the drug substance from the completed Module *3.2.S.5.*]

2.3.S.6 Container Closure System (common name, manufacturer)

(*) A brief description and discussion of the information, from *3.2.S.6* should be included. [Insert information on the container closure system for the drug substance from the completed Module *3.2.S.6.*]

2.3.S.7 Stability (common name, manufacturer)

(*) This section should include a summary of the studies undertaken (conditions, batches, container closure system, analytical procedures) and a brief discussion of the results and conclusions and of the proposed storage conditions and shelf life, as described in *3.2.S.7.1*. [Insert the summarized information from the completed Module *3.2.S.7.1*.] If filing a CTA/CTA-A, submit all available information that has been compiled to-date.

The post-approval stability protocol, as described in *3.2.S.7.2*, should be included. [Insert the post-approval stability protocol and stability commitment from the completed Module *3.2.S.7.2*.]

A summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided. [Insert the tabulated summary (or graphical representation where appropriate) of the results from the stability studies from the completed Module *3.2.S.7.3*.]

2.3.P DRUG PRODUCT (PROPRIETARY NAME, DOSAGE FORM)

2.3.P.1 Description and Composition of the Drug Product (proprietary name, dosage form)

(*) Information from *3.2.P.1* should be provided. [Insert information and a description of the drug product from the completed Module *3.2.P.1*.]

(*) *Composition from 3.2.P.1 should be provided.* [Insert the composition of the drug product from the completed Module *3.2.P.1.*]

(*) If filing a CTA/CTA-A for a placebo-controlled study, a qualitative list of the ingredients in the placebo should be provided.

2.3.P.2 Pharmaceutical Development (proprietary name, dosage form)

(*) A discussion of the information and data from 3.2.P.2 should be presented. [Insert the combined summary of the information and data from the completed Module *3.2.P.2.1* to *3.2.P.2.6*, except the tabulated summary from Module *3.2.P.2.2.1* on the composition of the formulations used in clinical trials and the batches affected.] If filing a CTA/CTA-A, submit all available information that has been compiled to-date.

(*) A confirmation that none of the non-medicinal ingredients (excipients) which appear in the final product are prohibited for use in drugs by the Canadian Food and Drugs Act and Regulations should be provided under Notes to Reviewer in Section 1.0.7. [Insert the confirmation from the completed Module *3.2.P.2.1.2,* under *Excipients*.]

(*) *A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.* [Insert a tabulated summary of the composition of the formulations used in clinical trials and the batches affected from the completed Module *3.2.P.2.2.1*, under *Formulation Development*.]

2.3.P.3 Manufacture (proprietary name, dosage form)

Information from 3.2.P.3 should include:

- (*) Information on the manufacturer(s). [Insert the completed Module *3.2.P.3.1*.]

- (*) Information from *3.2.P.3.2* on the batch formula and batch size should be provided. For a product under development, the proposed batch size range should not exceed ± 20% of the current manufacturing experience with the drug product, unless supported by pharmaceutical development data. [Insert the tabulated summary on the batch formula from the completed Module *3.2.P.3.2*.]

- (*) A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate

quality. [Insert the description of the manufacturing process, controls, and reprocessing procedures from the completed Module *3.2.P.3.3*.]

- (*) A flow diagram, as provided under *3.2.P.3.3*. [Insert the process flow diagram from the completed Module *3.2.P.3.3*.]

- (*) A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. [Insert the information from the completed Module *3.2.P.3.4* as follows: A summary of critical manufacturing steps, process controls, and acceptance criteria; A discussion of the process control(s) selected for each critical manufacturing step and justification of the proposed acceptance criteria.]

  Highlight critical process intermediates, as described in *3.2.P.3.4*; [Insert information on the quality and control of intermediates isolated during the process from the completed Module *3.2.P.3.4*.]

- A brief description of the process validation and/or evaluation, as described in *3.2.P.3.5*. [Insert a summary of the process validation and/or evaluation studies from the completed Module *3.2.P.3.5*.]

2.3.P.4 Control of Excipients (proprietary name, dosage form)

(*) A brief summary on the quality of excipients, as described in 3.2.P.4, should be included along with the following statement in the QOS-B or CPID-B: "A confirmation, that none of the non-medicinal ingredients (excipients) which appear in the final product are prohibited for use in drugs by the Canadian Food and Drugs Act and Regulations". [Insert the information from the completed Module 3.2.P.4 as follows: The specifications for excipients from *3.2.P.4.1*; The justification for proposed excipient specifications, where appropriate from *3.2.P.4.4*; The tabulated summary of excipients from human or animal origin that are used from *3.2.P.4.5*; A summary of the novel excipients that are used from *3.2.P.4.6.*]

2.3.P.5 Control of Drug Product (proprietary name, dosage form)

(*) *Specification(s) from 3.2.P.5.1 should be provided.* [Insert the specification(s) for the drug product from the completed Module *3.2.P.5.1*.]

(*) A brief summary of the justification of the specification(s), (*) a summary of the analytical procedures, a summary of the validation of analytical procedures, and characterisation of impurities should be provided. [Insert the information from the completed Module 3.2.P.5 as follows: A summary of the analytical procedures from *3.2.P.5.2*; A summary of the validation of analytical procedures from *3.2.P.5.3*; A summary of the characterisation of impurities from *3.2.P.5.5*; and a summary of the justification of the specification from *3.2.P.5.6*.]

(*) The drug product standard declared by the company responsible for routine release testing and post-market stability testing should be provided. [Insert the declared drug product standard from the completed Module *3.2.P.5.1*.]

(*) *A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate, should be included.* [Insert the written summary of the batch analyses, the tabulated summary (or graphical representation where appropriate) of results (other than impurities) from in vivo study batches and recent production batches from the completed Module *3.2.P.5.4*.] If filing a CTA/CTA-A, submit all available information, on all batches produced to-date and for which complete manufacturing documentation has been provided.

2.3.P.6 Reference Standards or Materials (proprietary name, dosage form)

(*) Information from 3.2.P.6 (tabulated presentation, where appropriate including name(s) and use(s)) should be included. [Insert information on the reference standards or reference materials used for testing of the drug product from the completed Module 3.2.P.6.]

2.3.P.7 Container Closure System (proprietary name, dosage form)

(*) A brief description and discussion of the information in 3.2.P.7 should be included. [Insert information on the container closure system for the drug product from the completed Module 3.2.P.7.]

2.3.P.8 Stability (proprietary name, dosage form)

(*) A summary of the studies undertaken (conditions, batches, container closure system, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf life and, if applicable, in-use storage conditions and shelf life should be given. [Insert the summarized information from the completed Module *3.2.P.8.1*.] If filing a CTA/CTA-A, submit all available information that has been compiled to-date.

The post-approval stability protocol, as described in *3.2.P.8.2*, should be provided. [Insert the post-approval stability protocol and stability commitment from the completed Module *3.2.P.8.2*.]

(*) *A summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included.* [Insert the tabulated summary (or graphical representation where appropriate) of the results from the stability studies from the completed Module *3.2.P.8.3*.]

2.3.A APPENDICES

2.3.A.1 Facilities and Equipment (common/proprietary name, manufacturer)

(*For products from human sources only), a summary of facility information, including relevant product-contact equipment cleaning procedures along with the validation of these cleaning procedure described under 3.2.A.1 should be included. [Insert a summary of the facilities and equipment information from the completed Module 3.2.A.1.]

2.3.A.2 Adventitious Agents Safety Evaluation (common name, dosage form, manufacturer)

(*) A discussion on measures implemented to control endogenous and adventitious agents in production should be included. [Insert the information from the completed Module 3.2.A.2 as follows: A summary of the measures used to avoid and control non-viral adventitious agents during production, from under For non-viral adventitious agents; A summary of the measures used to test, evaluate, and eliminate the potential risks of viral adventitious agents during production, from under For viral adventitious agents; A summary of the measures used to select, test, evaluate, and eliminate the potential risks of adventitious agents in any materials of animal or human origin that are used, from under Materials of Biological Origin; A brief summary of the virological test(s) conducted during manufacturing, at which step(s) and intermediate(s), and the conclusion of the testing results, from under Testing at appropriate stages of production; A brief summary of the virological test(s) conducted on unprocessed bulk and the conclusion of the testing results, from under Viral Testing of Unprocessed Bulk; The rationale and action plan for assessing viral clearance, the results and evaluation of the viral clearance studies, from under Viral Clearance Studies.]

(*) *A tabulated summary of the reduction factors for viral clearance from 3.2.A.2 should be provided.* [Insert the tabulated summary of the reduction factors for viral clearance from the completed Module 3.2.A.2, under Viral Clearance Studies.]

(*) A detailed calculation of the estimated particles /dose, where relevant, should be provided. [Insert the calculation of estimated particles/ dose, where relevant, from the completed Module 3.2.A.2, under Viral Clearance Studies.]

2.3.A.3 Excipients

(*) A summary of the excipients described under 3.2.A.3, their suitability for use, and a discussion on their potential risk(s), should be provided. [Insert the summary of the excipients from the completed Module 3.2.A.3.]

2.3.R REGIONAL INFORMATION

A brief description of the information specific for the region, as provided under "3.2.R" should be included, where appropriate. In Canada, this may be limited to a summary of the

medical device provided under 3.2.R.2 and the biosimilarity assessment between a biosimilar biologic drug and a reference biologic drug provided under 3.2.R.5, as applicable.

End of "Module 2.3 QOS Guidance"

2.3 Module 3: Quality

2.3.1 Content and Extent of Supporting Quality Information

A copy of all of the supporting Quality information and data should be submitted in Module 3. This information should consist of Modules 3.1 TABLE OF CONTENTS, 3.2 BODY OF DATA, and 3.3 LITERATURE REFERENCES. Module 3.2 is further subdivided into 3.2.S DRUG SUBSTANCE, 3.2.P DRUG PRODUCT, 3.2.A APPENDICES, and 3.2.R REGIONAL INFORMATION.

The Quality information submitted under Module 3 should be up-to-date, comprehensive, appropriately detailed, relevant, and to the extent sufficient to support the approval of a New Drug Submission (NDS), Supplemental New Drug Submission (SNDS), Notifiable Change (NC) or Biological Drug Identification Number Application (DIN-B), pursuant to section C.08.004 of the Food and Drug Regulations, and which complies with the current regulatory requirements under Sections C.08.002 and C.08.003, and Part C- Divisions 1, 1A, 2, and 4, (as appropriate) of the Food and Drug Regulations. Similarly, for a Clinical Trial Application (CTA) or Clinical Trial Application-Amendment (CTA-A), the quality information should support the requirements, pursuant to Part C- Division 5 of the Food and Drug Regulations.

The applicant is encouraged to provide the information, which is relevant to their particular product, when completing Module 3.2 BODY OF DATA of the drug submission in CTD format. In some subsections under Module 3.2 BODY OF DATA, where specific ICH Quality guidelines are referenced, the relevant information described in those technical guidelines should be provided under the appropriate subsections in the BODY OF DATA, to help ensure that the submission fulfils the screening requirements.

A properly completed Module 3 will facilitate preparation of the Quality Overall Summary - Biologics (QOS-B (Schedule D drugs)) and Certified Product Information Document – Biologics (CPID-B (Schedule D drugs)), as well as, expedite the drug submission review process.

2.3.2 Preparation of the Supporting Quality Information

The ICH Harmonised Tripartite Guidance, The Common Technical Document Module 3: Quality section, the Common Technical Document-Quality Questions and Answers/ Location Issues document, and the Guidance on the Supporting Quality Information (provided under *2.3.5*), should be referred to for preparing the Quality information required under Module 3 for a biotherapeutic or blood product. However, in this Guidance on the Supporting Quality Information, the ICH guideline on preparing the quality information under Module 3 has

been reproduced, streamlined by excluding the ICH guideline for NCE products, and integrated with the Health Canada guidance to conveniently provide the applicant with a consolidated guidance document on how to put together the quality information for a Canadian drug submission. This guidance covers topics not necessarily described by any existing ICH technical quality guidelines and it contains information, which should be considered during drug development as well as, for the preparation of a drug submission.

The Guidance on the Supporting Quality Information provides additional Health Canada guidance, clarification, where necessary, illustrative examples, and references to Health Canada Quality guidance documents to further assist the sponsor. Under Module 3.2.R, REGIONAL INFORMATION, additional information, which should be submitted for a Canadian drug submission, is also identified. In a few subsections of Module 3.2 BODY OF DATA, where other Canadian regulatory information should be provided, this information is identified with a dagger (†) symbol.

To ease the preparation of the QOS-B and CPID-B, the applicant is encouraged to follow, in particular, this Guidance on the Supporting Quality Information regarding the preparation of summarized information or tabulated summaries, and which is easily identified by, "[Copy information to QOS-B or CPID-B under a certain section]".

NOTE: A reference to the Health Canada Guidance on Good Manufacturing Practices (for Schedule D drugs) is meant to be included under almost every section of Module 3.2 BODY OF DATA. However, in order to minimize the size of the Guidance on the Supporting Quality Information, the GMP guidance was not referenced under most sections, although the applicant should refer to it when preparing Module 3.

In some cases, it may be appropriate to separate or repeat sections within a single drug submission in the CTD format. In these cases, the identifiers (provided in brackets) after a section or subsection heading (e.g. name, manufacturer, dosage form) should be completed to help distinguish the repeated sections. The applicant should consult the Common Technical Document-Quality Questions and Answers/ Location Issues document, for further guidance. The following examples are included to better illustrate this:

For Allergenic Extracts

For traditional Allergenic Extracts, the starting material, the pretreatment and the extraction of the allergen should be included as part of 3.2.S (Drug Substance) under the various sections as appropriate. Production of the final extract should be summarized in 3.2.P (Drug Product). For new forms of modified allergenic extracts, contact BRDD for advice.

For a drug product containing more than one drug substance:

(E.g. Biotech substance "X", Biotech substance "Y", such as with a biological immunotoxin which is not used as a vaccine.) The entire Module 3.2.S DRUG SUBSTANCE for one drug substance should be followed by the entire Module 3.2.S DRUG SUBSTANCE for the next

drug substance, then followed by a single Module 3.2.P DRUG PRODUCT. The name of the Drug Substance should be included in the heading of all applicable sections and subsections, to distinguish clearly the information for each Drug Substance.

e.g. 3.2.S DRUG SUBSTANCE ("X", MANUFACTURER ABC);
3.2.S DRUG SUBSTANCE ("Y", MANUFACTURER ABC);
3.2.P DRUG PRODUCT ("XY", Liquid Preparation).

In the case of a radiolabeled monoclonal antibody for example, the applicable biotherapeutic and radiopharmaceutical formats for Module 3.2.S DRUG SUBSTANCE and the Radiopharmaceutical format for Module 3.2.P DRUG PRODUCT, should be used accordingly.

For a drug substance and/or drug product which is manufactured by more than one manufacturer and where there are differences in the Quality information associated with each manufacturer:

(E.g. Manufacturer "A" and Manufacturer "B", both fill the drug product using different equipment and separate facilities.) The name of the manufacturer should be included in the heading of any affected sections and subsections, to distinguish clearly the drug substance and/or drug product information for each manufacturer, as the case may be. The numbering of the sections and subsections in this case should still be sequential.

e.g. *3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form, Manufacturer "A");*
3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form, Manufacturer "B");
3.2.P.3.4 Controls of Critical Steps and Intermediates (name, dosage form, Manufacturer "A and B"); (In section 3.2.P.3.4, the information is the same regardless of the manufacturer, so it only needs to be stated once.)
3.2.A.1 Facilities and Equipment (name, Manufacturer "A");
3.2.A.1 Facilities and Equipment (name, Manufacturer "B");

For a Drug Product with more than one dosage form or a Drug Product supplied with a reconstitution diluent without a Drug Identification Number (DIN):

(E.g. lyophylisate, liquid.) The entire Module 3.2.P DRUG PRODUCT for one dosage form and/or diluent (as the case may be), should be followed by the entire Module 3.2.P DRUG PRODUCT for the next dosage form and/or diluent (as the case may be). The name of the dosage form should be included in the headings of all corresponding sections and subsections, to distinguish clearly the quality information for each dosage form and/or diluent, as the case may be.

e.g. 3.2.P DRUG PRODUCT (NAME, "lyophylisate");
3.2.P DRUG PRODUCT ("Reconstitution Diluent for lyophylisate");
3.2.P DRUG PRODUCT (NAME, "liquid form").

For a drug product which has more than one formulation:

(E.g. "Original" Formulation: 2 mg substance "X"+ 125 mg Substance "Y"; "Ultra" Formulation: 10 mg substance "X"+ 500 mg Substance "Y";) Identification of the formulation should be included in the heading of any affected sections and subsections, to distinguish clearly the information for each formulation and drug product. The numbering of the sections and subsections in this case should still be sequential.

e.g. *3.2.P.2.2.1 Formulation Development (name, "Original formulation", dosage form)*;
3.2.P.2.2.1 Formulation Development (name, "Ultra formulation", dosage form);...***3.2.P.2.3,....3.2.P.3.2 Batch Formula (name, "Original formulation", dosage form)***;
3.2.P.3.2 Batch Formula (name, "Ultra formulation", dosage form);...3.2.P.3.3,...

For drug products with more than one type of packaging:

(E.g. bottle, syringe.) Identification of the packaging should be included in the heading of any affected sections and subsections, to distinguish clearly the information for each drug product. The numbering of the sections and subsections in this case should still be sequential.

e.g. 3.2.P DRUG PRODUCT (NAME, "liquid form")- 3.2.P.1 Description and Composition of the Drug Product (name, "liquid form", 5 ml glass bottle); 3.2.P.1 Description and Composition of the Drug Product (name, "liquid form", 2 ml plastic syringe)

For a drug product with more than one strength:

(E.g. 100 IU/vial, 500 IU/vial, 1000 IU/vial.) Identification of the strength should be included in the heading of any affected sections, subsections, and/or presentation of the information, to distinguish clearly the information for each strength. The numbering of the sections and subsections in this case should still be sequential.

e.g. different strengths are identified within the following table under ***3.2.P.5.1 Specification(s) (name, dosage form)***:

Test	Test Method	Specification(s):		
		100 IU/vial	500 IU/vial	1000 IU/vial
Potency Assay	Specific Binding Assay	90-110 IU/vial	450-550 IU/vial	800-1200 IU/vial
Total Protein	Micro-Kjeldahl	< 1.0 mg/ml	< 1.0 mg/ml	< 1.0 mg/ml
pH	Potentiometric	6.6-7.4	6.6-7.4	6.6-7.4

Where additional guidance is necessary for completing this Module, the applicant should consult with the ORA.

2.3.3 Presentation of the Supporting Quality Information

To ease the access to information and migration through the drug submission, the applicant should consult this guidance document and the *ICH Guideline M4: Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use - Annex: Granularity Document* (https://database.ich.org/sites/default/files/M4_R4__Guideline.pdf) for further guidance on the definition of a document in Module 3, document pagination and segregation, section numbering within documents, and table of contents formatting.

With respect to the definitions of a document within Module 3.2.R REGIONAL INFORMATION (for Canada), a separate document should be provided for 3.2.R.2 Medical Devices, 3.2.R.4 Yearly Biologic Product Report (YBPR), 3.2.R.5 Assessment of similarity, 3.2.R.6 On-Site Evaluation, and 3.2.R.8 Product Lifecycle Management Information whereas one document or multiple documents (e.g. one for each batch) can be submitted for Modules 3.2.R.1 Production Documentation and 3.2.R.3 Lot Release Documentation.

Where identical or relevant information has been provided in another section of Module 3 or where there is supporting or related information from other Modules of the submission, the applicant is encouraged to clearly cross-reference to the location of that information. Cross-referencing should be sufficiently detailed, to allow the appropriate information to be easily located within the drug submission, and it should correspond to the pagination and unique header or footer identifiers on each page.

Where regional information may need to be provided under the Drug Substance (3.2.S) or Drug Product (3.2.P) sections, the information could be integrated within the section or document (e.g. where only minimal information is required) or provided in a separate document, attachment, or Volume to that section (e.g. in the case of a lengthy study report or a Site Master File). The approach taken should also be in accordance to the guidance on the definition of a Quality document - See the *ICH Guideline M4: Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use* under the *Annex: Granularity Document* (https://database.ich.org/sites/default/files/M4_R4__Guideline.pdf). This flexibility in approach is intended to minimize problems associated with pagination and cross-referencing in global submissions.

2.3.4 Submission of the Supporting Quality Information

For an NDS, Module 3 information should be submitted in its entirety.

For an SNDS or an NC, which includes changes in the Quality information, only those subsections that are affected by the change(s) need to be submitted, although the CTD format and numbering for those subsections should be maintained, and cross-referencing to relevant information from any prior-related submissions should be included.

For a Biological DIN Application (DIN-B), Module 3 information should be submitted for only the required subsections or parts for a DIN-B, depending upon the product, and on a case-by-case basis. The applicant should consult with the ORA for additional guidance on the technical data requirements for their particular drug submission, if necessary.

For a Clinical Trial Application (CTA), if there is a significant amount of supporting information to those subsections or parts which have an asterisk (*) beside the guidance or heading in Module 2.3, this information should be submitted separately in the appropriate Module 3 section.

It is understood that depending on the stage of drug development, a limited amount of information may be available for a CTA; in which case, the sponsor should provide whatever data is available at that time. With subsequent CTA filings for the same drug (e.g. Phase 2 or 3 studies), where much of the quality information may be similar, the sponsor is encouraged to build upon the historical information (e.g. Phase 1 study), by making any necessary revisions or adding relevant information to update the submission and clearly identifying the changes (e.g. with use of coloured text or a different font). A summarized chronology of the changes made to the manufacturing process should be maintained throughout each clinical study phase of drug development to the NDS stage. Sponsors may complete and submit additional Module 3 subsections, as that information becomes available during the course of drug development (e.g. Phase 2 and 3 CTAs), or as advance preparation of an NDS.

Similarly for Clinical Trial Application-Amendments (CTA-A), with changes to the Quality information, if there is extensive supporting information to those subsections or parts which

have an asterisk (*) beside the guidance or heading in Module 2.3, this information should be submitted separately in the affected Module 3 section(s), and the appropriate subsection numbering and CTD format should be maintained.

References:

ICH Guidelines:
- M4
- M4Q
- M4Q Quality & Answers / Location Issues

Health Canada Guidance Documents:

- Post-Notice of Compliance (NOC) Changes: Quality Document
- Guidance for Clinical Trial Sponsors- Clinical Trial Applications (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/clinical-trial-sponsors-applications.html)
- Organisation and Document Placement for Canadian Module 1 (available upon request).
- Clinical Trial Applications in eCTD format (available upon request).
- Preparation of Regulatory Activities in the Electronic Common Technical Document (eCTD) Format (available upon request).
- Guidance Document - Preparation of Regulatory Activities in Non-eCTD Format (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/common-technical-document/updated-guidance-document-preparation-regulatory-activities-non-ectd-electronic-only-format.html)

2.3.5 Guidance on the Supporting Quality Information

The text following the section titles is intended to be explanatory and illustrative only. The content of these sections should include relevant information described in existing ICH guidance documents, but harmonised content is not available for all sections. The "Body of Data" in this guidance document merely indicates where the information should be located. Neither the type nor extent of specific supporting data has been addressed in this guidance document, and both may depend upon regional guidance.

Start of "Module 3: Quality Guidance"

3.1 TABLE OF CONTENTS OF MODULE 3

A Table of Contents for the filed application should be provided.

3.2 BODY OF DATA

3.2.S DRUG SUBSTANCE[1] (NAME, MANUFACTURER)

3.2.S.1 General Information (name, manufacturer)

3.2.S.1.1 Nomenclature (name, manufacturer)

Information on the nomenclature of the drug substance should be provided. For example: [Copy this information to the QOS-B under 2.3.S.1.]

- Recommended International Nonproprietary Name (INN);
- Compendial name if relevant;
- Chemical name(s);
- Company or laboratory code;
- Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN), and
- Chemical Abstracts Service (CAS) registry number.

3.2.S.1.2 Structure (name, manufacturer)

A brief description of the structural formula(e) if possible should be provided, plus of other drug(s) of similar structure, where useful. [Copy this information to the QOS-B under 2.3.S.1.]

3.2.S.1.3 General Properties (name, manufacturer)

A list should be provided of physicochemical and other relevant properties of the drug substance, including biological activity. [Copy this information to the QOS-B under 2.3.S.1.]

References:

ICH Guideline:
- Q6B

3.2.S.2 Manufacture (name, manufacturer)

3.2.S.2.1 Manufacturer(s) (name, manufacturer)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided in a tabulated summary (see example below). If more than one testing site, the

[1] For a drug product containing more than one drug substance, the information requested for part "S" should be provided in its entirety for each drug substance.

compendial and/or non-compendial test(s) performed at each site should be listed. [Copy this tabulated summary to the QOS-B under 2.3.S.2: Information on the manufacturer; Copy this information to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Manufacturer(s)*]

Name and address	Responsibilities
Facility A	Drug substance manufacturer In-process controls testing Release testing including all compendial methods and non-compendial methods.
Facility B	Manufacturer and storage of the Master and Working cell banks Stability testing (e.g., Appearance, SE-HPLC, SDS-PAGE)
Facility C	Stability testing (e.g., Potency, RP-HPLC) Unprocessed bulk testing

3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

For Conventional Biotherapeutic products:

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For example: Information should be provided on the manufacturing process, which typically starts with starting material extraction, purification and modification reactions, filling, storage and shipping conditions.

The applicant should provide an overall process flow diagram, including the relevant information described under each step below (e.g., in-process control testing, size and scale of equipment, batch size, pooling, and hold times). [Copy this information to the QOS-B under 2.3.S.2: Flow diagram; Copy this information to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Description of Manufacturing Process and Process Controls*: flow diagram.]

Batch(es) and scale definition

An explanation of the batch numbering system, including information regarding any pooling of extracts or intermediates and batch size or scale should be provided. Since

pooling may occur at more than one step, it may be more appropriate to describe the batch size and scale under the respective step(s), both within the flow diagram(s) and in the detailed description. [Copy this information to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls Copy the information on the batch size or scale to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Description of Manufacturing Process and Process Controls*: flow diagram.]

Extraction, Purification, modification reactions and formulation (when applicable)

A flow diagram should be provided that illustrates the purification steps (i.e., unit operations) from the extraction of the starting material up to the step preceding filling of the drug substance. All steps and intermediates and relevant information for each stage (e.g., volumes, pH, critical processing time, holding times, temperatures and elution profiles and selection of fraction, storage of intermediate, if applicable) should be included. Critical steps for which specifications are established as mentioned in *3.2.S.2.4* should be identified. [Copy this information to the QOS-B under 2.3.S.2: Flow diagram; Copy this information to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Description of Manufacturing Process and Process Controls*: flow diagram.]

A description of each process step in the flow diagram should be provided. The description should include information on, for example, scale, buffers and other reagents (details provided in *3.2.S.2.3*), excipient, major equipment (details provided in 3.2.A.1), and materials. For materials such as filter membranes and chromatography resins, information for conditions of use and reuse should also be provided (equipment details in 3.2.A.1; validation studies for the reuse and regeneration of columns and membranes in *3.2.S.2.5*). The description should include process controls (including in-process tests and operational parameters) with acceptance criteria for process steps, equipment and intermediates. (Details in *3.2.S.2.4*.) [Copy this information to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls.]

Reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described. [Copy this information to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls. (Details should be given in 3.2.S.2.5.); Copy this information to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Description of Manufacturing Process and Process Controls*: flow diagram.]

Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided. [Copy this information to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls.] (Details on shipping and storage provided in *3.2.S.2.4*.)

Filling, storage and transportation (shipping)

A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be

provided. (Details in *3.2.S.2.4*.) [Copy this information to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls.]

The container closure system(s) used for storage of the drug substance (details in 3.2.S.6) and storage and shipping conditions for the drug substance (details and supporting stability data in *3.2.S.7.3*) should be described. [Copy the information on the container closure system(s) for the drug substance to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls.]

References:

ICH Guidelines:

- Q5A and Q6B

Health Canada Guidance Documents:

- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)

For Biotherapeutic products:

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For example: Information should be provided on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage and shipping conditions.

Rather than providing separate flow diagrams for the fermentation and purification processes, the applicant may consider providing an overall process flow diagram, including the relevant information described under each step below (e.g., in-process control testing, size and scale of equipment, batch size, pooling, and hold times). [Copy this information to the QOS-B under 2.3.S.2: Flow diagram; Copy this information to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Description of Manufacturing Process and Process Controls*: flow diagram.]

Batch(es) and scale definition

An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided. Since pooling may occur at more than one step, it may be more appropriate to describe the batch size and scale under the respective step(s), both within the flow diagram(s) and in the detailed description. [Copy this information to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls; Copy the information on the batch size or

scale to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Description of Manufacturing Process and Process Controls*: flow diagram.]

Cell culture and harvest

A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (e.g. cells contained in one or more vials(s) of the Working Cell Bank up to the last harvesting operation. The diagram should include all steps (i.e., unit operations) and intermediates. Relevant information for each stage, such as population doubling levels, cell concentration, volumes, pH, cultivation times, holding times, and temperature, should be included. Critical steps and critical intermediates for which specifications are established (as mentioned in 3.2.S.2.4) should be identified. [Copy this information to the QOS-B under 2.3.S.2: Flow diagram; Copy this information to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Description of Manufacturing Process and Process Controls:* flow diagram.]

A description of each process step in the flow diagram should be provided. Information should be included on, for example, scale; culture media and other additives (details provided in 3.2.S.2.3); major equipment (details provided in 3.2.A.1); and process controls, including in-process tests and operational parameters, process steps, equipment and intermediates with acceptance criteria (details provided in 3.2.S.2.4). Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided. (Details on shipping and storage provided in 3.2.S.2.4.) [Copy this information to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls.]

Purification, modification reactions and formulation (when applicable)

A flow diagram should be provided that illustrates the purification steps (i.e., unit operations) from the crude harvest(s) up to the step preceding filling of the drug substance. All steps and intermediates and relevant information for each stage (e.g., volumes, pH, critical processing time, holding times, temperatures and elution profiles and selection of fraction, storage of intermediate, if applicable) should be included. Critical steps for which specifications are established as mentioned in 3.2.S.2.4 should be identified. [Copy this information to the QOS-B under 2.3.S.2: Flow diagram; Copy this information to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: Description of Manufacturing Process and Process Controls: flow diagram.]

A description of each process step (as identified in the flow diagram) should be provided. The description should include information on, for example, scale, buffers and other reagents (details provided in 3.2.S.2.3), excipient, major equipment (details provided in 3.2.A.1), and materials. For materials such as filter membranes and chromatography resins, information for conditions of use and reuse also should be provided (equipment details in 3.2.A.1; validation studies for the reuse and regeneration of columns and membranes in 3.2.S.2.5.) The description should include process controls (including in-

process tests and operational parameters) with acceptance criteria for process steps, equipment and intermediates. (Details in 3.2.S.2.4.) [Copy this information to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls.]

Reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described. [Copy this information to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls; Copy this information to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Description of Manufacturing Process and Process Controls*: flow diagram.] (Details should be given in 3.2.S.2.5.)

Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided. [Copy this information to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls.] (Details on shipping and storage provided in 3.2.S.2.4.)

Filling, storage and transportation (shipping)

A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be provided. (Details in 3.2.S.2.4.) [Copy this information to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls.]

The container closure system(s) used for storage of the drug substance (details in 3.2.S.6) and storage and shipping conditions for the drug substance (details and supporting stability data in 3.2.S.7.3) should be described. [Copy the information on the container closure system(s) for the drug substance to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls.]

References:

ICH Guidelines:

- Q5A, Q5B and Q6B

Health Canada Guidance Documents:

- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)Guide to validation – drugs and supporting activities (GUIDE-0029)

For Blood products:

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For example: Information should be provided on the manufacturing process, including plasma pooling, fractionation, filling, storage and shipping conditions.

Batch(es) and scale definition

An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided. Since pooling may occur at more than one step, it may be more appropriate to describe the batch size and scale under the respective step(s), both within the flow diagram(s) and in the detailed description. [Copy this information to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls; Copy the information on the batch size or scale to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Description of Manufacturing Process and Process Controls*: flow diagram.]

Fractionation and/or Purification

A flow diagram should be provided that illustrates the manufacturing route from blood or plasma pooling, through fractionation and/or purification, up to the step preceding filling of the drug substance. Any manufacturing steps or processes that are intentionally included for viral inactivation and/or removal, should be clearly identified. The diagram should include all steps (i.e., unit operations) and intermediates. Relevant information for each stage, such as volumes, pH, critical processing time, holding times, temperatures and elution profiles and selection of a fraction, yield calculations at critical manufacturing steps, and storage of any intermediate(s), if applicable, should be included. Critical steps and critical intermediates for which specifications are established (as mentioned in 3.2.S.2.4) should be identified. [Copy this information to the QOS-B under 2.3.S.2: Flow diagram; Copy this information to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: Description of Manufacturing Process and Process Controls: flow diagram.]

A description of each process step in the flow diagram should be provided. Information should be included on, for example, scale; buffers, reagents, and other additives (details provided in 3.2.S.2.3); major equipment (details provided in 3.2.A.1); and process controls, including in-process tests and operational parameters, process steps, equipment and intermediates with acceptance criteria (details provided in 3.2.S.2.4). For materials such as filter membranes and chromatography resins, information for conditions of use and reuse also should be provided (equipment details in 3.2.A.1; validation studies for the reuse and regeneration of columns and membranes in 3.2.S.2.5.).

Reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described (details should be given in 3.2.S.2.5.) Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided (details on shipping and storage provided in 3.2.S.2.4.) [Copy this information to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls; Copy this information to the

CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Description of Manufacturing Process and Process Controls*: flow diagram.]

Filling, storage and transportation (shipping)

A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be provided. (Details in 3.2.S.2.4.) [Copy this information to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls.]

The container closure system(s) used for storage of the drug substance (details in 3.2.S.6) and storage and shipping conditions for the drug substance (details and supporting stability data in 3.2.S.7.3) should be described. [Copy the information on the container closure system(s) for the drug substance to the QOS-B under 2.3.S.2: Description of the manufacturing process and controls.]

References:

ICH Guidelines:

- Q5A and Q6B

Health Canada Guidance Documents:

- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)
- Guide to validation – drugs and supporting activities (GUI-0029)

3.2.S.2.3 Control of Materials (name, manufacturer)

Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically sourced materials, this can include information regarding the source, manufacture, and characterisation. (Details in 3.2.A.2.) For clarification, this is an introductory paragraph, which generally applies to each of the subdivided types of materials identified below.

References:

ICH Guidelines:

- Q6B and Q11

Control of Source and Starting Materials of Biological Origin

Summaries of viral safety information for biologically-sourced materials should be provided. (Details in 3.2.A.2.)

References:

Health Canada Guidance Documents:

- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)

Detailed information on the suitability for use of the biological raw materials that are utilized as processing aids (e.g. auxiliary material), should be provided, including their source, country of origin, manufacturer, method of manufacture, microbiological controls performed, and specifications. For example, a tabulated summary could be used: [Copy the completed tabulated summary to the QOS-B under 2.3.S.2: Description of the Source and Starting material and raw materials of biological origin used in the manufacture of the drug substance including the Master Cell Bank(s) (MCBs) and Working Cell Bank(s) (WCBs) used in the manufacture of the drug substance; Copy the completed tabulated summary to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Control of Materials*: Description of the Source and Starting material and raw materials of biological origin used in the manufacture of the drug substance.]

Biological Raw Material	Biological Source	Country of Origin	Manufacturer	Step	Suitability for Use

The use of Transmissible Spongiform Encephalopathy (TSE) Certificates of Suitability to the monographs of the European Pharmacopoeia (CEPs) issued by the European Directorate for the Quality of Medicines and Healthcare of the Council of Europe (EDQM) may be provided to support raw materials, auxiliary materials and reagents at risk of transmitting BSE/TSE agents.

For Conventional Biotherapeutic products

Detailed information on the suitability of the starting material from which the conventional biotherapeutic is extracted should be provided. This information should include the country of origin of the donor, selection criteria for the donors and all quality control testing of the starting material plus its storage and shipping conditions. [Copy this information to the QOS-B under 2.3.S.2: Description of the Source and Starting material and raw materials of biological origin used in the manufacture of the drug substance]

References:

ICH Guidelines:
- Q5A and Q5C

For Biotherapeutic products

Source, history, and generation of the cell substrate

Information on the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop the Master Cell Bank should be provided as described in Q5B and Q5D. This information could also include a flow diagram on the derivation of the cell substrate. [Copy this information to the QOS-B under 2.3.S.2: Description of the Source and Starting material and raw materials of biological origin used in the manufacture of the drug.] Any supporting literature references should be provided under 3.3 LITERATURE REFERENCES and the titles(s) cross-referenced under this section.

References:

ICH Guidelines:
- Q5B and Q5D

Cell banking system, characterisation, and testing

Information on the cell banking system, quality control activities, and cell line stability during production and storage (including procedures and a detailed summary of the qualification protocols used to generate the Master and Working Cell Bank(s)) should be provided as described in Q5B and Q5D. This information could also include, for example: details of testing performed on all cell banks, and a flow diagram on the derivation of the cell banks with details on cell concentration, volume, and the number of aliquots prepared. In addition, a tabulated summary of the specifications, and results of characterisation and testing performed on the cell banks should be provided. [Copy this information to the QOS-B under 2.3.S.2: Description of the Source and Starting material and raw materials of biological origin used in the manufacture of the drug substance; Copy the name of the Master and Working Cell Bank(s) to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Control of material*.]]

References:

ICH Guidelines:
- Q5A, Q5B, Q5C and Q5D

For Blood products

Origin and Collection of the Source and Starting Material

The origin of the blood, serum, or plasma units (e.g. human or animal-derived, recovered, or source plasma) should be described. Detailed information on all the blood or plasma collection establishments and subcontractors used, including their name and address, the country or countries from where blood or plasma donations are collected, information on the prevalence of relevant infectious disease markers in the population from which they collect from, compared to that found in North American sources, and recent (dated) documentation related to regulatory certification, authorization, licensing and/or inspection of the blood or plasma collection establishment(s), should be provided. The regulatory authority (ies) involved should be identified.

Information on the controls, good manufacturing practices, and processes used for blood or plasma collection (e.g. standard operating procedures, deferral procedures associated with reactive test results, donor re-entry algorithms, hold periods, quarantine and disposal of unsuitable material, the system for maintaining donor information and for conducting tracebacks and lookbacks, procedures related to the ongoing review of epidemiological, post-donation and seroconversion information, the control of labelling, shipping and storing of individual units, the mechanism and frequency for conducting internal quality audits and review, and the system for maintaining appropriate blood or plasma collection facilities), should be provided. [Copy this information to the QOS-B under 2.3.S.2: Description of the Source and Starting material and raw materials of biological origin used in the manufacture of the drug substance.]

If applicable, a cross-reference to a master file (MF) should be made under this section and a Letter of Authorization to allow Health Canada to review this information should be provided under Module 1.2.6. Applicants should consult the appropriate regional Guidance Documents and/or regulatory authorities for additional guidance.

References:

Health Canada Guidance Documents:

- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)
- Guidance Document: Blood Regulations

Donor Suitability, Testing, and Screening

Detailed information on the selection or deferral of the donor (e.g. donor history assessment, written and oral questionnaire, physical examination, and informed consent form) and on the screening of the individual blood or plasma donations for the appropriate bloodborne transmissible disease markers (e.g. for human-derived blood or plasma: HBsAg, antibodies to HIV-1, antibodies to HIV-2, antibodies to HCV, HIV-1 p24 Ag,

HB core Ag, syphilis, and NAT for HCV RNA, HIV-1 RNA, HAV RNA, HBV DNA, Parvovirus B19 DNA) using validated and appropriate test methods with respect to sensitivity, for different genotypes and specificity, should be provided to support the suitability of the source or starting material used and to qualify the donor. Information on the test methods, including the name, manufacturer, generation, and acceptance limit of a test kit, and the date when it was approved by which regulatory authority(ies), should be provided. For example, a tabulated summary could be used:

TD Marker	Test	Manufacturer	Generation	Acceptance Limit	Regulatory Approval

[Copy this information to the QOS-B under 2.3.S.2: Description of the Source and Starting material and raw materials of biological origin used in the manufacture of the drug substance.]

If applicable, a cross-reference to a Master File (MF) should be made under this section and a Letter of Authorization to allow Health Canada to review this information should be provided under Module 1.2.6. Applicants should consult the appropriate regional Guidance Documents and/or regulatory authorities for additional guidance.

References:

Health Canada Guidance Documents:

- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)
- Guidance Document: Blood Regulations
- Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements

Additional Safety Measures on the Source and/or Starting Material

Information on additional precautions which are taken by the manufacturer(s) of the blood product, in collaboration and contract with the blood or plasma collection establishment(s), to ensure the safety and quality of the blood or plasma used for further manufacturing (e.g. traceback and lookback systems to track individual donations from donor to blood collection establishment to a lot of drug product and vice versa, post-market and clinical follow-up of recipients for viral transmission and other adverse events), should be provided.

[Copy this information to the QOS-B under 2.3.S.2: Description of the Source and Starting material and raw materials of biological origin used in the manufacture of the drug substance.]

If applicable, a cross-reference to an MF should be made under this section and a Letter of Authorization to allow Health Canada to review this information should be provided under Module 1.2.6. Applicants should consult the appropriate regional Guidance Documents and/or regulatory authorities for additional guidance.

References:

Health Canada Guidance Documents:
- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)
- Guidance Document: Blood Regulations
- Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements

3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

Critical Steps:

Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in *3.2.S.2.2* of the manufacturing process to ensure that the process is controlled should be provided. This information should be provided in detail. If identical analytical procedures are used for controlling critical steps, intermediates, and the drug substance, a cross-reference should be made to *3.2.S.4.2 Analytical Procedures* and *3.2.S.4.3 Validation of the Analytical Procedures* information, as applicable. [A summary of this section should be provided in the QOS-B under 2.3.S.2: Selection of manufacturing steps, process controls and acceptance criteria; Copy this summary to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Controls of Critical Steps and Intermediates*: Summary of critical manufacturing steps.]

A discussion of the process control(s) selected for each critical manufacturing step and justification of the proposed acceptance criteria should also be provided. [Copy this information to the QOS-B under 2.3.S.2: Discussion of selection and justification of manufacturing steps, process controls and acceptance criteria.]

Intermediates:

For Conventional Biotherapeutic products and Biotherapeutic products

Detailed information on the quality and control of intermediates isolated during the process should be provided.

References:

ICH Guidelines:
- Q6B and Q11

Stability data supporting storage conditions of intermediate(s) should be provided in detail. [A summary of the quality, control, and storage conditions of intermediates isolated during the process, should be provided in the QOS-B under 2.3.S.2: Highlight critical intermediates; Copy this summary to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Controls of Critical Steps and Intermediates*: Highlight critical intermediates.]

References:

ICH Guidelines:

- Q5C

For Blood products

Detailed information on the quality and control of intermediates isolated during the process should be provided. This should include information regarding the pooling of individual plasma units (e.g. the total blood or plasma pool size, taking into consideration, any initial pooling, combined with any blending of separate batches and/or the use of any blood or plasma-derived materials which are utilized as processing aids during manufacturing) and the screening of the blood or plasma pool(s) for the appropriate known bloodborne transmissible markers (e.g. for human plasma pools: HBsAg, antibodies to HIV-1, antibodies to HIV-2, antibodies to HCV, and NAT for HCV RNA, HIV-1 RNA, HAV RNA, HBV DNA, Parvovirus B19 DNA) using validated and appropriate test methods, (A summary of the viral testing information in 3.2.A.2.) Information on the test methods, including the name, manufacturer, generation, and acceptance limit of a test kit, and the date when it was approved by which regulatory authority(ies), should be provided. For example, a tabulated summary could be used:

TD Marker	Test	Manufacturer	Generation	Acceptance Limit	Regulatory Approval

References:

ICH Guidelines:

- Q6B and Q11

Health Canada Guidance Documents:

- Guidance Document: Blood Regulations

Stability data supporting storage conditions of intermediate(s) should be provided in detail. [A summary of the quality, control, and storage conditions of intermediates isolated during the process, should be provided in the QOS-B under 2.3.S.2: Highlight

critical intermediates; Copy this summary to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Controls of Critical Steps and Intermediates*: Highlight critical intermediates.]

References:

ICH Guideline:
- Q5C

3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

Process validation and/or evaluation studies for aseptic processing and sterilisation should be included.

Sufficient information should be provided on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification).

The information provided in the study report should support the current manufacturing process and scale proposed for commercial use, including data to demonstrate consistency in yield and production, and degree of purity. The process validation study report and the protocols for the extent of reuse and regeneration of columns and membranes should be provided, including in-process test results and data from relevant manufacturing batches, to demonstrate consistency in the quality and safety of the drug substance during production. The suitability of any proposed reprocessing procedures described in *3.2.S.2.2* and the criteria for reprocessing of any intermediate or the drug substance should be discussed. If adjuvants are added to the drug substance, information and data from the adsorption and desorption study should be submitted.

[A summary of the process validation and evaluation studies should be provided. in the QOS-B under 2.3.S.2: Description of process validation.]

The plan for conducting the study should be described and the results, analysis and conclusions from the executed study(ies) should be provided. The analytical procedures and corresponding validation should be cross-referenced (e.g., *3.2.S.2.4*, *3.2.S.4.3*) or provided as part of justifying the selection of critical process controls and acceptance criteria.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in 3.2.A.2.

References:

ICH Guideline:
- Q11

Health Canada Guidance Documents:
- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)
- Cleaning Validation Guidelines (GUIDE-0028)
- Validation Guidelines for Pharmaceutical Dosage Forms (GUI-0029)

3.2.S.2.6 Manufacturing Process Development (name, manufacturer)

The developmental history of the manufacturing process, as described in *3.2.S.2.2*, should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g., nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number (and subsequential drug product batch numbers), manufacturing date, scale, and use (e.g., stability, nonclinical, reference material) in relation to the change, should be provided.

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 Q5E and Q6B for additional guidance). A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. A cross-reference to the location of these studies in other sections of Module 3 (e.g. Stability, Control of Drug Substance or Drug Product) and/or in other modules of the submission should be included. [Copy this information to the QOS-B under 2.3.S.2: Summary of major manufacturing changes.]

Reference should be made to the drug substance batch analysis data provided in section *3.2.S.4.4*, to the in-process control tests batch analysis data provided in *3.2.S.2.5*, and to the batch analysis data on impurities provided in *3.2.S.3.2*.

[A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency should be provided in the QOS-B under 2.3.S.2: Summary of major manufacturing changes.]

References:

ICH Guidelines:
- Q5E, Q6B, Q9, Q10 and Q11

3.2.S.3 Characterisation (name, manufacturer)

3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

For desired product and product-related substances, details should be provided on primary, secondary, tertiary and/or higher-order structure, post-translational forms (e.g., glycoforms), biological activity, purity, and immunochemical properties, when relevant. For conventional biotherapeutic products provide this information to the extent possible.

[A summarized description of the desired product and product-related substances and a summary of general properties, characteristic features and characterisation data, such as primary and higher order structure and biological activity, should be provided in the QOS-B under 2.3.S.3: Description of desired product; Copy this summary to the CPID-B (Schedule D drugs) under Characterisation: *Elucidation of Structure and other Characteristics*. For the CPID-B, the table below may be used to summarize the information.]

Quality attribute	Analytical Method	Summary of Results

References:

ICH Guideline:
- Q6B

3.2.S.3.2 Impurities (name, manufacturer)

Information on impurities should be provided. All potential impurities, including degradation products arising from manufacturing, storage or found in stability study batches, should be described regardless of whether they have been detected in any batches. The actual impurity levels detected (including quantities found in clinical, toxicological, bioavailability, and proposed commercial batches) should be reported, for example, using a summary table: [Copy the tabulated summary to the QOS-B under 2.3.S.3: Tabulated summary of data; Copy the tabulated summary to CPID-B (Schedule D drugs) under Characterisation: *Impurities*.]

Impurity	Proposed Limit	Use of Batches and Lot Number								
		Batches used in toxicological studies			Batches used in clinical studies			Proposed commercial batches		
Product-Related Impurities										
Process-Related Impurities										
Residual Solvents										

The information should also include a discussion of results that are close to or outside limits. A rationale should be provided for the choice of tests used, the proposed limits and their qualification, including a control strategy for each impurity (cross-reference to S.2.6 or S.4.5 can be made as appropriate). Proposed limits should be supported by evidence where applicable (e.g. toxicological limits, clinical experience, NOAEL, PDE etc.).

If not provided in Section S.4.5, provide a rationale for excluding any impurity test(s) from routine release testing due to trace levels, where applicable. This information may be reported using the following summary tables [Copy this information to the QOS-B under 2.3.S.3: How impurity levels are qualified.]

Process-related Impurity or residual solvent/inorganic impurity	**Source of impurity** (i.e. manufacturing step or raw material, solvent)	**Control Strategy and Proposed Limit** (i.e. monitored as IPC, controlled as a release specification, demonstration of removal)	**Maximum allowable amount** (if applicable)	**Supporting evidence to ensure safety and/or scientific justification** (if applicable)

Product-related Impurity	Control Strategy and Proposed Limit (i.e. monitored as IPC, controlled as a release specification, demonstration of removal)	Supporting evidence to ensure safety and/or scientific justification (if applicable)

References:

ICH Guidelines:
- Q3C, Q5C and Q6B

3.2.S.4 Control of Drug Substance (name, manufacturer)

3.2.S.4.1 Specification (name, manufacturer)

The specifications for the drug substance should be provided. For example, the specifications could be presented using a table with the test parameter(s), method type, method code, source, and acceptance limit(s) at release, shelf-life or for both. [Copy this information to the QOS-B under 2.3.S.4 Control of Drug Substance: Specification from 3.2.S.4.1; Copy this information to the CPID-B (Schedule D drugs) under Control of Drug Substance: *Specification*: Specification.]

The drug substance standard (e.g. Schedule B, Manufacturer's, Professed) declared by the company responsible for routine release testing should be specified. [Copy this information to the QOS-B under 2.3.S.4 Control of Drug Substance: Drug substance standard declared; Copy this information to the CPID-B (Schedule D drugs) under Control of Drug Substance: *Specification*: Drug substance standard declared.]

References:

ICH Guideline:
- Q6B

3.2.S.4.2 Analytical Procedures (name, manufacturer)

The analytical procedures used for testing the drug substance should be provided (i.e., the SOP).

[A summary of the analytical procedures should be provided in the QOS-B under 2.3.S.4 Control of Drug Substance: Summary of analytical procedures. This may be combined with the summary of the validation of analytical procedures (*3.2.S.4.3*) and a summary of the justification of the specification (*3.2.S.4.5*).]

References:

ICH Guideline:
- Q6B

3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided. This information should also include validation protocols and reports.

[A summary of the validation of analytical procedures should also be provided in the QOS-B under 2.3.S.4 Control of Drug Substance: Summary of validation. This may be combined with the summary of the analytical procedures (*3.2.S.4.2*) and a summary of the justification of the specification (*3.2.S.4.5*).]

References:

ICH Guidelines:
- Q2(R1) and Q6B

3.2.S.4.4 Batch Analyses (name, manufacturer)

Description of batches and results of batch analyses should be provided for the validation lots. This description should include the batch number, production scale, date of manufacture, production site, manufacturing process and use. Confirmation should be provided that the batch analysis data results reported in the submission for the validation batches were generated by the company responsible for routine testing of the drug substance. If any tests described under *3.2.S.4.2* were not conducted (and if Certificates of Analysis have not been provided), the information should include a description of the incomplete analyses. Results that are close to or outside of current limits should be discussed. Any changes in specifications, test methods, limits and validation, and a rationale for those changes over the production history should also be described. A description of the lot numbering system (if not fully described under *3.2.S.2.2* Batch and Scale Definition) should be provided. [Copy a summary of this information to the QOS-B under 2.3.S.4 Control of Drug Substance: Tabulated summary of batch analyses.]

References:

ICH Guidelines:
- Q3C, Q3D and Q6B

3.2.S.4.5 Justification of Specification (name, manufacturer)

Justification for the drug substance specifications should be provided. Although the drug substance specifications are only one part of the total control strategy, this section is appropriate to summarize the overall drug substance control strategy (or identify where the control strategy is located in the submission).

[A summary of the justification of the drug substance specification should be provided in the QOS-B under 2.3.S.4 Control of Drug Substance: Summary of justification of the specification(s). This may be combined with the summary of the analytical procedures (*3.2.S.4.2*) and the summary of the validation of analytical procedures (*3.2.S.4.3*).]

References:

ICH Guidelines:
- Q3C, Q3D, Q6B and Q11

3.2.S.5 Reference Standards or Materials (name, manufacturer)

Information on the reference standards or reference materials used for testing of the drug substance, including the procedures and a detailed summary of protocols for the qualification of future reference standards, should be provided. [Copy this information to the QOS-B under 2.3.S.5. Reference Standards or Materials; Copy this information to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Reference Standards or Materials*]

At the time of filing of a marketing application (NDS or DIN-B), it is recommended that a two-tiered reference standard program be in place.

References:

ICH Guideline:
- Q6B

3.2.S.6 Container Closure System (name, manufacturer)

A description of the container closure system(s) should be provided, including the supplier(s), identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description, size and identification (and critical dimensions with drawings, where appropriate). This description should include the information appearing on the label(s). [Copy this information to the QOS-B under 2.3.S.6. Container Closure System; Copy this information to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Container Closure System*.]

Non-compendial methods (with validation) used to release the container closure system should be included, where appropriate.

For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

References:

Health Canada Guidance Document:

- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)

3.2.S.7 Stability (name, manufacturer)

3.2.S.7.1 Stability Summary and Conclusions (name, manufacturer)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and shelf life. As clarification, "results" refers to the conclusions from the various studies, addressing storage conditions tested, container closure system, batch number, completed and proposed test stations, study test parameters and frequency of testing, recommended shipping and monitoring conditions, and the proposed storage conditions and shelf life. [Copy this summarized information to the QOS-B under 2.3.S.7: Summary of the studies; Copy this summarized information to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: Stability: *Stability Summary and Conclusions*.]

Information on the stability batches and batch lineage should also be provided. This information may be reported using the following summary table.

Drug substance batch number	Batch Designation (Phase of development or Process Validation)	Batch size	Manufacturing location and process	Manufacturing date	Type of stability study	Stability data currently available

References:

ICH Guidelines:
- Q1A, Q1B, Q5C and Q6B

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)

The post-approval stability protocol and annual stability commitment should be provided. [Copy this information to the QOS-B under 2.3.S.7: Post-approval stability protocol; Copy this summarized information to the CPID-B (Schedule D drugs) under S DRUG SUBSTANCE: *Post-approval Stability Protocol and Stability Commitment*]

References:

ICH Guidelines:
- Q1A, Q5C and Q7

3.2.S.7.3 Stability Data (name, manufacturer)

Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be cross-referenced to other sections of Module 3 that contain this information or included under this section, if the information is different from that described under *3.2.S.4.1*, *3.2.S.4.2*, and *3.2.S.4.3*. Any incomplete analyses should be explained.

A tabulated summary (with graphical representation, where appropriate) of the results from the stability studies, should also be provided. [Copy the completed tabulated summary to QOS-B under 2.3.S.7: Tabulated summary]

References:

ICH Guidelines:
- Q1A, Q1B, Q1E, Q1F, Q2(R1), Q5C, Q6B and Q7

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.1 Description and Composition of the Drug Product (name, dosage form)

A description of the drug product and its composition should be provided. The information provided should include, for example [Copy this information to the QOS-B under 2.3.P.1.]:

- Description of the dosage form;

- Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications)

- Description[2] of accompanying reconstitution diluent(s); and

- Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

References:

ICH Guideline:
- Q6B

3.2.P.2 Pharmaceutical Development (name, dosage form)

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. It should include a summary and discussion of the risk assessment for nitrosamine impurities in the drug product. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Any supporting literature references should be provided under 3.3 LITERATURE REFERENCES and the titles(s) cross-referenced under this section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

In addition to the detailed information, the applicant should also consider providing a combined summary of the information and data provided under *3.2.P.2.1* to *3.2.P.2.6*, except the tabulated summary provided under *3.2.P.2.2.1* on the composition of the formulations used in clinical trials and the batches affected. [Copy this summary to the QOS-B under 2.3.P.2: discussion of information.]

References:

[2] For a drug product supplied with a reconstitution diluent(s) without a DIN, information on the diluent(s) should be provided in a separate part "P", as appropriate.

ICH Guidelines:
- Q6B, Q8, Q9 and Q10

3.2.P.2.1 Components of the Drug Product (name, dosage form)

3.2.P.2.1.1 Drug Substance (name, dosage form)

The compatibility of the drug substance with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product should be discussed.

For combination products, the compatibility of drug substances with each other should be discussed.

3.2.P.2.1.2 Excipients (name, dosage form)

The choice of excipients (including adjuvants) listed in 3.2.P.1, their concentration, their characteristics that can influence the drug product performance should be discussed relative to their respective functions.

3.2.P.2.2 Drug Product (name, dosage form)

3.2.P.2.2.1 Formulation Development (name, dosage form)

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the commercial formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate, under both this section and in Module 4.

A tabulated summary of the composition of the formulations used in clinical trials and the batches numbers associated with the formulations should also be provided. For example, [Copy the completed tabulated summary to the QOS-B under 2.3.P.2: Tabulated summary of the composition.]

Composition of Formulation or Code#	Batch#(s)	Strength	Type of Study Used In

3.2.P.2.2.2 Overages (name, dosage form)

Any overages in the formulation(s) described in 3.2.P.1 should be justified.

3.2.P.2.2.3 Physicochemical and Biological Properties (name, dosage form)

Parameters relevant to the performance of the drug product, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity should be addressed.

References

ICH Guideline:

- Q8

3.2.P.2.3 Manufacturing Process Development (name, dosage form)

The selection and optimisation of the manufacturing process described in *3.2.P.3.3*, in particular its critical aspects, should be explained. Where relevant, the method of sterilisation should be explained and justified.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the commercial process described in *3.2.P.3.3* that can influence the performance of the product should be discussed. Comparison of the different manufacturing process(es) in tabular format or using flow diagram(s) is also recommended.

A cross-reference should be made to other sections and/or Modules where related study data may be found, such as to the drug product batch analysis data provided in section *3.2.P.5.4*, to the in-process control tests batch analysis data provided in *3.2.P.3.5*, and to the batch analysis data on impurities provided in *3.2.P.5.5*.

3.2.P.2.4 Container Closure System (name, dosage form)

The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching, and moisture or vapour transmission) safety of materials of construction (e.g. corking studies for multi-dose vials), and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product). In discussing the choice of materials and compatibility of the materials of construction, a summary of the pharmacopoeial tests for elastomeric components and plastics, and maintenance of pH, should be included. The results from the suitability and compatibility studies should be provided.

References:

ICH Guideline:
- Q8

Health Canada Guidance Document:
- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)

3.2.P.2.5 Microbiological Attributes (name, dosage form)

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives (e.g. multi-dose vials). For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed. The study design and results of any antimicrobial and preservative effectiveness and integrity of container closure system testing should be provided.

3.2.P.2.6 Compatibility (name, dosage form)

The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labelling.

Compatibility studies should be conducted for the proposed commercial drug product having contact with administration or closed system transfer devices (e.g., intravenous administration sets) and should include extractables and leachable studies with the dosage devices. Worst case administration sets or closed system transfer devices to be used for compatibility studies may be determined based on a risk assessment. Compatibility study design including dose preparation and administration components, type of materials, stress conditions, hold times, temperatures, stability indicating tests and results should also be provided.

3.2.P.3 Manufacture (name, dosage form)

3.2.P.3.1 Manufacturer(s) (name, dosage form)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided in a tabulated summary. If more than one testing site, the compendial and/or non-compendial test(s) performed at each site should be listed. The name of the importer/distributor along with the name of the assay used for identity testing, as applicable, should also be provided in the CPID-B. For testing sites located in non-MRA countries, technical transfer data for tests performed for importation in Canada should be provided in Module 3. [Copy this tabulated summary to the QOS-B under 2.3.P.3:

Information on the manufacturer; Copy this information to the CPID-B (Schedule D drugs) under P.3.1 DRUG PRODUCT: *Manufacturer(s)*.]

Name and address	Responsibilities
Facility A	Drug product manufacturer Packaging (primary and secondary)/Labelling In-process controls testing Release testing including all compendial methods and non-compendial methods Stability testing (e.g., Potency, RP-HPLC)
Facility B	Secondary packaging/Labelling Stability testing (e.g., sterility, SE-HPLC, SDS-PAGE)
Facility C	Importer and distributor (Enzymatic activity used as identity test) (†)

(†) This information can be provided in the CPID-B only.

3.2.P.3.2 Batch Formula (name, dosage form)

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards. The anticipated range of commercial (production) batch sizes should be described in the batch formula(e)and should be based on available manufacturing experience. A tabulated summary of this information may be provided. For example, [Copy the completed tabulated summary to the QOS-B under 2.3.P.3: Information on batch formula; Copy the completed tabulated summary to the CPID-B (Schedule D drugs) under P DRUG PRODUCT: *Batch Formula*.]

Master Formula# or Code		
Date Master Formula Approved		
Strength (Label Claim)		
Batch Size (# of dosage units)		
Ingredient, Test Standard	**Quantity per batch**	**Quantity per batch**
TOTAL (where applicable)		

For a product under development, the proposed range should not exceed ± 20% of the current manufacturing experience with the drug product, unless supported by pharmaceutical development data.

3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified. [Copy this information to the QOS-B under 2.3.P.3: Flow diagram; Copy this information to the CPID-B (Schedule D drugs) under P DRUG PRODUCT: *Description of Manufacturing Process and Process Controls.]*

A narrative description of the manufacturing process, including packaging, which represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogeniser) and working capacity, where relevant. [Copy this information to the QOS-B under 2.3.P.3: Description of manufacturing process and controls.]

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section *3.2.P.3.4*. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated. [Copy this information to the QOS-B under 2.3.P.3: Description of manufacturing process and controls.]

Proposals for the reprocessing of materials should be justified. [Copy this information to the QOS-B under 2.3.P.3: Description of manufacturing process and controls; Copy this information to the CPID-B (Schedule D drugs) under P DRUG PRODUCT: *Description of Manufacturing Process and Process Controls.*] Any data to support this justification should be either cross-referenced to *3.2.P.3.5* or filed in this section (*3.2.P.3.3*).

Additionally, see 3.2.A.1 for facilities, if appropriate.

References:

ICH Guideline :
- Q6B

Health Canada Guidance Document:
- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)

3.2.P.3.4 Controls of Critical Steps and Intermediates (name, dosage form)

Critical Steps:

Tests and acceptance criteria should be provided (with justification, including experimental data) for process controls performed at the critical steps identified in *3.2.P.3.3* of the manufacturing process, to ensure that the process is controlled. This information should be provided in detail.

If identical analytical procedures are used for controlling critical steps, intermediates, excipients, and the drug product, a cross-reference should be made to *3.2.P.4.2 Analytical Procedures* for Control of Excipients and/or *3.2.P.5.2 Analytical Procedures* for Control of Drug Product information. A cross-reference should also be made to *3.2.P.4.3 Validation of the Analytical Procedures* for Control of Excipients and *3.2.P.5.3 Validation of the Analytical Procedures* for Control of the Drug Product information, as applicable.

[A summary of critical manufacturing steps, process controls performed, and acceptance criteria, should be provided in the QOS-B under 2.3.P.3: Selection of critical manufacturing steps, process controls and acceptance criteria; Copy this summary to the CPID-B (Schedule D drugs) under P DRUG PRODUCT: *Controls of Critical Steps and Intermediates*: Summary of critical manufacturing steps, process controls, and acceptance criteria.]

A discussion of the process control(s) selected for each critical manufacturing step and justification of the proposed acceptance criteria should also be provided or cross-referenced to 3.2.P.2. [Copy this information to the QOS-B under 2.3.P.3: Discussion of the selection and justification of critical manufacturing steps, process controls and acceptance criteria.]

Intermediates:

Information on the quality and control of intermediates isolated during the process should be provided. [Copy this information to the QOS-B under 2.3.P.3: Highlight critical process intermediates; Copy this information to the CPID-B (Schedule D drugs) under P DRUG PRODUCT: *Controls of Critical Steps and Intermediates*: highlight critical process intermediates.]

References:

ICH Guidelines:

- Q2(R1) and Q6B

3.2.P.3.5 Process Validation and/or Evaluation (name, dosage form)

Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilisation process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2.A.2, if necessary.

The information provided in the study report should support the current manufacturing process proposed for commercial use, including in-process test results and data from relevant manufacturing batches to demonstrate consistency in yield and production, and degree of purity. The validation study report for the extent of reuse and integrity of sterile filter membranes should be provided, including data to demonstrate consistency in the quality and safety of the drug product.

The suitability of any proposed reprocessing procedures described in *3.2.P.3.3* and the criteria for reprocessing of any intermediate or the drug substance should be discussed.

If adjuvants are added to the drug product, information and data from the adsorption and desorption study should be submitted.

[A summary of the process validation and evaluation studies should be provided in the QOS-B under 2.3.P.3: Description of process validation.]

References:

ICH Guideline:
- Q6B

Health Canada Guidance Documents:
- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)
- Cleaning Validation Guidelines (GUIDE-0028)
- Process Validation: Aseptic Processes for Pharmaceuticals (GUI-0029)
- Validation Guidelines for Pharmaceutical Dosage Forms

3.2.P.4 Control of Excipients (name, dosage form)

3.2.P.4.1 Specifications (name, dosage form)

The specifications for excipients should be provided. [Copy the specifications for excipients to the QOS-B under 2.3.P.4: Control of Excipients]

(†) For any (non-novel) non-compendial excipient (or adjuvant) for which detailed information is necessary to support its quality, safety, suitability for use, and 'approvability', this information should be submitted under 3.2.A.3 according

to the drug substance and/or drug product CTD format, with a cross-reference to 3.2.A.3 and/or a cross-reference to supporting safety data (nonclinical and/or clinical details in Modules 4 and/or 5) under this section. Additionally, if applicable, a cross-reference to a Master File (MF) should be made under this section and a Letter of Authorization to allow Health Canada to review this information should be provided under Module 1.2.6. Applicants should consult the appropriate regional guidance documents and/or regulatory authorities for additional guidance.

References:

ICH Guideline:
- Q6B

Health Canada Guidance Documents
- Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements

3.2.P.4.2 Analytical Procedures (name, dosage form)

The analytical procedures used for testing the excipients should be provided, where appropriate. This includes analytical procedures used for testing excipients of human or animal origin and novel excipients.

(†) The justification for analytical procedures used for testing non-Schedule B (i.e. non-pharmacopoeial) excipients and novel excipients, should also be provided.

References:

ICH Guideline:

- Q2(R1) and Q6B

3.2.P.4.3 Validation of Analytical Procedures (name, dosage form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

(†) E.g. for non-Schedule B (i.e. non-pharmacopoeial) excipients and Schedule B ingredients with supplementary tests not required by the monograph(s).

References:

ICH Guidelines:
- Q2(R1) and Q6B

3.2.P.4.4 Justification of Specifications (name, dosage form)

Justification for the proposed excipient specifications should be provided, where appropriate.

(†) E.g. for non-Schedule B (i.e. non-pharmacopoeial) and novel excipients. [Copy this information to the QOS-B under 2.3.P.4: Control of Excipients]

References:

ICH Guidelines:
- Q3C and Q6B

3.2.P.4.5 Excipients of Human or Animal Origin (name, dosage form)

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data). (Details in 3.2.A.2.) This information should also include the suitability for use, country of origin, manufacturer, and method of manufacture, and microbiological controls performed.

A tabulated summary of excipients of human or animal origin that are used, including the source, country of origin, manufacturer, and a brief description on the suitability for use based upon the controls evaluated (e.g. history, testing, screening), should also be provided. For example, the following table may be used. [Copy the completed tabulated summary to the QOS-B under 2.3.P.4: Control of Excipients; Copy the completed tabulated summary to the CPID-B (Schedule D drugs) under Control of Excipients: *Excipients of Human or Animal Origin*.]

Excipient	Biological Source	Country of Origin	Manufacturer	Suitability for Use

(†) For any excipient of human or animal origin which is a drug product in its own right and which is currently approved for sale in Canada, a brief description on its quality, safety, and suitability for use, and confirmation that it is an approved excipient, should be provided under this section.

For any excipient of human or animal origin which is not currently approved for sale in Canada, the detailed quality information necessary to support its quality, safety, suitability for use, and 'approvability', should be submitted under 3.2.A.3 according to the drug substance and/or drug product CTD format, with a cross-reference to 3.2.A.3 under this section. Additionally, if

applicable, a cross-reference to an MF should be made under this section and a Letter of Authorization to allow Health Canada to review this information should be provided under Module 1.2.6. Applicants should consult the appropriate regional guidance documents and/or regulatory authorities for additional guidance.

References:

ICH Guidelines:
- Q5A and Q6B

Health Canada Guidance Documents:
- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)
- Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/master-files-procedures-administrative-requirements.html)

3.2.P.4.6 Novel Excipients (name, dosage form)

For excipient(s) (including adjuvants) used for the first time in a drug product or by a new route of administration, full details of manufacture (including manufacturer(s)), characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical details in Modules 4 and/or 5) should be provided according to the drug substance and/or drug product CTD format. (Details in 3.2.A.3.)

(†) For any excipient which is currently approved for sale in Canada and which is used for the first time in a drug product or by a new route of administration, a brief description on its quality, detailed information on its safety, and suitability for use, and confirmation that it is an approved excipient, should be provided under this section.

For any novel excipient which is not currently approved for sale in Canada, the detailed information necessary to support its quality, safety, suitability for use, and 'approvability', should be submitted under 3.2.A.3 according to the drug substance and/or drug product CTD format, with a cross-reference to 3.2.A.3 under this section. Additionally, if applicable, a cross-reference to an MF should be made under this section and a Letter of Authorization to allow Health Canada to review this information should be provided under Module 1.2.6. Applicants should consult the appropriate regional guidance documents and/or regulatory authorities for additional guidance.

(†) A summary of the novel excipients that are used, including the source, manufacturer, and a brief discussion on the suitability for use based upon the

controls evaluated (e.g. history, testing), should also be provided. [Copy this information to the QOS-B under 2.3.P.4: Control of Excipients]

References:

Health Canada Guidance Documents:
- Guidance Document: Master Files (MFs) - Procedures and Administrative Requirements

3.2.P.5 Control of Drug Product (name, dosage form)

3.2.P.5.1 Specification(s) (name, dosage form)

The specification(s) for the drug product should be provided. This would be the specification used by the company(ies) responsible for routine release testing and post-market stability testing. The specification could be presented using for example, a table with the test parameter(s), method type, method code, source, and acceptance limit(s) at release, shelf-life or for both. [Copy this information to the QOS-B under 2.3.P.5: Specification(s) from *3.2.P.5.1*; Copy this information to the CPID-B (Schedule D drugs) under Control of Drug Product: *Specification(s)*: specification(s) for the drug product.]

The drug product standard (e.g. Schedule B, Manufacturers, Professed) declared by the company responsible for routine release testing and post-market stability testing should be specified. [Copy this information to the QOS-B under 2.3.P.5: Drug product standard declared; Copy this information to the CPID-B (Schedule D drugs) under Control of Drug Product: *Specification(s)*: Drug product standard declared.]

References:

ICH Guideline:
- Q6B

3.2.P.5.2 Analytical Procedures (name, dosage form)

The analytical procedures used for testing the drug product should be provided (i.e., the SOP). [A summary of the analytical procedures should also be provided in the QOS-B under 2.3.P.5: Summary of analytical procedures. This may be combined with the summary of the validation of analytical procedures (*3.2.P.5.3*), a summary of the characterisation of impurities (*3.2.P.5.5*), and a summary of the justification of the drug product specification (*3.2.P.5.6*).]

References:

ICH Guidelines:
- Q2(R1) and Q6B

3.2.P.5.3 Validation of Analytical Procedures (name, dosage form)

Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product should be provided. This information should also include validation protocols and reports.

[A summary of the validation of analytical procedures should be provided in the QOS-B under 2.3.P.5: Summary of validation. This may be combined with the summary of the analytical procedures *(3.2.P.5.2*), a summary of the characterisation of impurities (*3.2.P.5.5*), and a summary of the justification of the drug product specification *(3.2.P.5.6*).]

References:

ICH Guidelines:
- Q2(R1) and Q6B

3.2.P.5.4 Batch Analyses (name, dosage form)

A description of batches and results of batch analyses should be provided for the validation batches. This description should include the batch number, production scale, date of manufacture, production site, manufacturing process and use. Confirmation should be provided that the batch analysis data results reported in the submission for the validation batches were generated by the company responsible for routine testing of the drug product.

This information should include a description of any deviations from the master formula or any abnormalities observed during production of any batches; a description of any incomplete analyses, if the tests described under *3.2.P.5.2* were not conducted (and if Certificates of Analysis have not been provided); a summary of any changes in specifications (analytical procedures and validation, where appropriate), and a rationale for those changes over the production history. All results, including those that are close to or outside of current limits, should be discussed.

A description of the lot numbering system for the drug product, (if not fully described under *3.2.S.2.2 Batch(es) and scale definition*) should be provided. [Copy the summary of this information to the QOS-B under 2.3.P.5: Tabulated summary of batch analyses.]

A tabulated summary (or graphical representation where appropriate) of results (other than impurities) from in vivo (bioequivalence, pivotal clinical) study batches and recent production batches should also be provided. For example, [Copy the completed tabulated summary to the QOS-B under 2.3.P.5: Tabulated summary of batch analyses.]

References:

ICH Guidelines:
- Q3C and Q6B

3.2.P.5.5 Characterisation of Impurities (name, dosage form)

Information on the characterisation of impurities (including degradation products arising from manufacturing, storage, or detected in stability study batches) should be provided in detail, and the actual impurity levels detected (including quantities found in clinical, toxicological, bioavailability or pharmacokinetic (PK)/pharmacodynamic (PD), and proposed commercial batches) should be reported, for example using a summary table, if not previously provided in *3.2.S.3.2 Impurities*.

The information should also include a discussion of results that are close to or outside limits. A rationale should be provided for the choice of tests used, the proposed limits and their qualification (cross-reference to *3.2.P.2* or *3.2.P.5.6* can be made as appropriate). These limits should be set taking into account the totality of what will be administered to the patient (i.e. in combination with other drugs, diluent or IV infusion solution). A rationale for excluding any impurity test(s) from routine release testing due to trace levels should also be provided, where applicable.

A summary of the characterisation of impurities (provided either under *3.2.P.5.5* or under *3.2.S.3.2*) should also be provided. (This may be combined with the summary of the analytical procedures (*3.2.P.5.2*), validation of analytical procedures (*3.2.P.5.3*), and a summary of the justification of the drug product specification (*3.2.P.5.6*).) [Copy this summary to the QOS-B under 2.3.P.5: Characterisation of impurities.]

References:

ICH Guidelines:
- Q5C and Q6B

3.2.P.5.6 Justification of Specification(s) (name, dosage form)

Justification for the proposed drug product specification(s) should be provided. Although the drug product specification is only one part of the total control strategy, this section is appropriate to summarize the overall drug product control strategy.

[A summary of the justification of the drug product specification should be provided in the QOS-B under 2.3.P.5: Summary of justification of specification(s). This may be combined with the summary of the analytical procedures (*3.2.P.5.2*), validation of analytical procedures (*3.2.P.5.3*), and a summary of the characterisation of impurities (*3.2.P.5.5*).]

References:

ICH Guideline:
- Q6B

3.2.P.6 Reference Standards or Materials (name, dosage form)

Information on the reference standards or reference materials used for testing of the drug product, including the procedures and a detailed summary of the protocols for the qualification of future reference standards, should be provided, if not previously provided in "3.2.S.5 Reference Standards or Materials". [Copy this information to the QOS-B under 2.3.P.6; Copy this information to the CPID-B (Schedule D drugs) under P DRUG PRODUCT: *Reference Standards or Materials*.]

At the time of filing of a marketing application (NDS or DIN-B), it is recommended that a two-tiered reference standard program be in place.

References:

ICH Guideline:
- Q6B

3.2.P.7 Container Closure System (name, dosage form)

A description of the container closure system(s) should be provided, including the supplier(s), identity of materials of construction of each primary packaging component and its specification. The specifications should include description, size and identification (and critical dimensions, including neck opening size for vials, with drawings where appropriate). [Copy this information to the QOS-B under 2.3.P.7; Copy this information to the CPID-B (Schedule D drugs) under P DRUG PRODUCT: *Container Closure System*.]

Non-compendial methods (with validation) used to release the container closure system(s) should be included where appropriate.

For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in 3.2.P.2.

References:

Health Canada Guidance Document:
- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)

3.2.P.8 Stability (name, dosage form)

3.2.P.8.1 Stability Summary and Conclusion (name, dosage form)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf life, and, if applicable, in-use storage conditions and shelf life. As clarification, "results" refers to the conclusions from the various studies, addressing storage conditions tested, container closure system if different than that described in 3.2.P.7 and orientation, batch number, batch strength, completed and proposed test stations, study test parameters and frequency of testing, recommended shipping and monitoring conditions, and the proposed storage conditions and shelf life.. [Copy this summarized information to the QOS-B under 2.3.P.8: Summary of studies undertaken; Copy this summarized information to the CPID-B (Schedule D drugs) under P DRUG PRODUCT: Stability: *Stability Summary and Conclusion*.]

Information on the stability batches and batch lineage should also be provided. This information may be reported using the following summary table:

Drug product batch number	Batch Designation (Phase of development or Process Validation)	Manufacturing location and process	Manufacturing date	Related drug substance batch number(s)	Type of stability study	Orientation tested	Stability data currently available

References:

ICH Guidelines:
- Q1A, Q1B, Q5C and Q6B

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment (name, dosage form)

The post-approval stability protocol and annual stability commitment should be provided. [Copy this information to the QOS-B under 2.3.P.8: Post-approval stability protocol; Copy this information to the CPID-B (Schedule D drugs) under P DRUG PRODUCT: Stability: *Post-Approval Stability Protocol and Stability Commitment*.]

References:

ICH Guidelines:
- Q1A and Q5C

Health Canada Guidance Document:

- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)

3.2.P.8.3 Stability Data (name, dosage form)

Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included unless provided in other CTD sections. Any incomplete analyses should be explained.

A tabulated summary (with graphical representation, where appropriate) of the results from the stability studies, should also be provided. [Copy the completed tabulated summary to the QOS-B under 2.3.P.8: Tabulated summary.]

Information on impurities should be located in *3.2.P.5.5*.

References:

ICH Guidelines:

- Q1A, Q1B, Q1E, Q1F, Q2(R1), Q5C and Q6B

Health Canada Guidance:

- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment (name, manufacturer)

A diagram should be provided illustrating the manufacturing flow, including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas as well as the room classification. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product (e.g., a dedicated or multi-use suite should be specified.)

Information on all developmental or approved products (or alternatively the product types/classes) manufactured or manipulated in the same areas as the applicant's product, along with the cell line/expression system used for each product (e.g., *E.coli*, CHO), or source material (if applicable), including change over procedures if upstream processing is occurring in the facility, should be included, as applicable. [Copy this information to the CPID-B (Schedule D drugs) under A APPENDICES: *Facilities and Equipment*.]

A summary description of relevant product-contact equipment, and its use (dedicated or multi-use, manufacturing step(s) where it is used) should be provided. Information on preparation, cleaning, sterilisation, and storage of specified equipment and materials should be included, as appropriate.

Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment, where operations for the preparation of cell banks and product manufacturing are performed. A summary of the environmental monitoring program, including data from the last 12 months in classified areas, should be provided.

If the product is either fabricated in animals, sourced from animals, or animals are used in its testing and are housed in the facility, information on the animal housing quarantine procedures, the segregation of areas in which animal procedures are taking place, and confirmation of a sentinel program should also be provided.

[A summary of all facilities and equipment information described in this section should also be provided in the QOS-B under 2.3.A.1. Facilities and Equipment]

References:

Health Canada Guidance Documents:

- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)
- Cleaning Validation Guidelines (GUIDE-000028)
- Guide to validation – drugs and supporting activities (GUI-0029)

3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.

For non-viral adventitious agents:

Detailed information should be provided on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents, prions, bacteria, mycoplasma, and fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent.

If using well-established (e.g., pharmacopoeial) analytical procedures for the routine manufacturing control of adventitious agents, such as bacteria, mycoplasma, and fungi, the detailed information should be provided in the appropriate sections within Module 3.2.S and 3.2.P. If well-established (e.g., pharmacopoeial) analytical procedures are not

used, more detailed information regarding the analytical procedure(s) used should also be included in 3.2.S and 3.2.P.

[A summary of the measures used to avoid and control non-viral adventitious agents during production should be provided in the QOS-B under 2.3.A.2: Discussion on measures.]

References:

ICH Guidelines:

- Q5A, Q5D and Q6B

For viral adventitious agents:

Detailed information from viral safety evaluation studies should be provided in this section. Viral evaluation studies should demonstrate that the materials used in production, including any biological auxiliary materials (e.g. monoclonal antibodies used as affinity ligands for purification, or processing enzymes used to activate, or modify the product, are safe, and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable. The applicant should refer to Q5A, Q5D and Q6B, as applicable, for further guidance.

[A summary of the measures used to test, evaluate, and eliminate the potential risks of viral adventitious agents during production should be provided in the QOS-B under 2.3.A.2: Discussion on measures.]

Materials of Biological Origin

Information essential to evaluate the virological safety of materials of animal or human origin (e.g. biological fluids, tissue, organ, cell lines) should be provided. (See related information in *3.2.S.2.3*, and *3.2.P.4.5*.)

For cell lines, information on the selection, testing, and safety assessment for potential viral contamination of the cells and viral qualification of cell banks should also be provided. (See related information in 3.2.S.2.3.)

For blood products, information on the donor suitability, blood or plasma unit testing and screening for appropriate blood borne transmissible disease markers, and the safety assessment for potential non-viral and/or viral contamination of the source material, should also be provided. (See related information in 3.2.S.2.3.)

[A summary of the measures used to select, test, evaluate, and eliminate the potential risks of viral adventitious agents in any materials of animal or human origin that are used should also be provided in the QOS-B under 2.3.A.2: Discussion on measures. This may also include a tabulated summary as described below of the suitability for use of the

biological raw materials described in *3.2.S.2.3* and the excipients of human or animal origin described in *3.2.P.4.5*.]

Biological Material	Biological Source	Country of Origin	Manufacturer	Step	Suitability for Use

References:

ICH Guidelines:
- Q5A and Q5D

Health Canada Guidance Documents:
- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)
- Guidance Document: Blood Regulations

Testing at appropriate stages of production

The selection of virological tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk or post viral clearance testing) should be justified. The type of test, sensitivity and specificity of the test, if applicable, and frequency of testing should be included. Test results to confirm, at an appropriate stage of manufacture, that the product is free from viral contamination should be provided. The study report information should be provided in detail. (See related information in *3.2.S.2.4* and *3.2.P.3.4*.)

[A brief summary of the virological test(s) conducted during manufacturing (e.g., on cell substrate, unprocessed bulk or as post viral clearance testing), at which critical step(s) and intermediate(s), and the conclusion of the testing results should be provided in the QOS-B under 2.3.A.2: Discussion on measures.]

Viral Testing of Unprocessed Bulk (For Biotherapeutic and Conventional Biotherapeutic products)

In accordance with Q5A and Q6B, results for viral testing of unprocessed bulk should be included. The study report information should be provided in detail.

[A brief summary of the virological test(s) conducted on unprocessed bulk and the conclusion of the testing results should be provided in the QOS-B under 2.3.A.2: Discussion on measures.]

References:

ICH Guidelines:
- Q5A and Q6B

Viral Testing of Intermediates (For Blood products)

Results for viral testing of intermediates (e.g. plasma pools) should be included. (Details in 3.2.S.2.4). The study report information should be provided in detail.

[A brief summary of the virological test(s) conducted on unprocessed bulk and the conclusion of the testing results should be provided in the QOS-B under 2.3.A.2: Discussion on measures.]

References:

ICH Guidelines:
- Q5A and Q6B

Viral Clearance Studies

In accordance with Q5A, the rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. [Copy this information to the QOS-B under 2.3.A.2: Discussion on measures.] Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps that are capable of removing or inactivating viruses. The study report information should be provided in detail, including a description of the operational range of critical parameters used in the scale-down studies compared to those used in commercial-scale production. (See related information in *3.2.S.2.5* and *3.2.P.3.5*.)

References:

ICH Guidelines:
- Q5A

A tabulated summary of the reduction factors for viral clearance should also be provided. This should include viral reduction performed both with new and used resins, unless it can be justified that data for new resins are appropriate to leverage for aged resins. [Copy the completed tabulated summary to the QOS-B under 2.3.A.2: Tabulated summary of reduction factors; Copy the completed tabulated summary to the CPID-B (Schedule D drugs) under A APPENDICES: *Adventitious Agents Safety Evaluation: Tabulated summary of reduction factors*.]

Intermediate (Step)	Log_{10} Reduction Factor				
	Target or Model virus "A" tested	Target or Model virus "B" tested	Target or Model virus "C" tested	Target or Model virus "D" tested	Target or Model virus "E" tested
TOTAL log_{10} Reduction Factor					

The calculation of estimated particles per dose and , where relevant, should also be provided. The calculation should also be expressed as "one retroviral-like particle per number of doses". The detailed calculation should be performed based on a worst-case scenario. [Copy this information to the QOS-B under 2.3.A.2: Calculation of estimated particles/dose; Copy this information to the CPID-B (Schedule D drugs) under A APPENDICES: *Adventitious Agents Safety Evaluation: calculation of estimated particles/dose*.]

3.2.A.3 Excipients (name, dosage form)

Any extensive drug substance and/or drug product information which is necessary to support the quality, safety, suitability for use, and 'approvability' of any novel excipient, any (non-novel) non-compendial excipient, and/or any excipient of human or animal origin, should be provided in section 3.2.A.3. (See related information in *3.2.P.4.5* and/or *3.2.P.4.6*.)

[A summary of the excipients described under 3.2.A.3, their suitability for use, and a discussion on their potential risk(s) should be provided in the QOS-B under 2.3.A.3: Excipients]

3.2.R REGIONAL INFORMATION

Any additional drug substance and/or drug product information specific to each region should be provided in section 3.2.R of the application. Applicants should consult the appropriate regional guidance documents and/or regulatory authorities for additional guidance.

3.2.R.1 Production Documentation (for Canada)

3.2.R.1.1 Executed Batch Records (name, dosage form, manufacturer)

Executed batch records are not required at time of filing to support a marketing application (NDS or DIN-B) or any post-NOC changes (S/NDS, NC or DIN-B). However, these may be requested during review and should be available within 15 days upon

request. If requested, the documentation submitted for the executed batches should be for products manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. Any notations made by operators on the executed production documents should be clearly legible.

In cases where executed batch records are requested, the most current Master batch records should be submitted only when they are different from executed batch records. In this case, the Master batch record should be submitted in English or French along with a summary of the discrepancies and the rationale for the differences.

3.2.R.2 Medical Devices (for Canada) (name, dosage form)

For a drug product supplied with a medical device, a description of the device(s), including its application, manufacturer, and confirmation that it has been notified or approved for use with the Medical Devices Directorate at Health Canada should be provided.

For combination products, they may be classified as either medical devices or drugs according to the principal mechanism of action by which the claimed effect to purpose is achieved. Those combination products that have been classified as devices include drug coated devices such as catheters, pacemaker leads, drug impregnated devices. Those that have been classified as drugs include prefilled syringes, transdermal patches, red blood cell processing solution, implants whose primary purpose is to release a drug.

For those combination products classified as drugs, relevant product information should be provided as per this guidance document. Compliance with the international standards (e.g., ISO 13485 requirements) should be demonstrated, when applicable. Where the device forms part of the primary packaging (i.e. is in contact with the product during storage), it should be described under P.7.

If relevant, for novel medical devices used to deliver the dosage form that are external to the drug product (e.g. inhalation devices), a description and details of the composition and specifications should be provided. Data to demonstrate suitability of the administration device should also be provided. If the device is provided with the drug product, it should be described in the CPID-B.

References:

Health Canada Guidance Document:

- Drug/Medical Device Combination Products (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/policies/drug-medical-device-combination-products.html)
- Policy on Drug/Medical Device Combination Products - Decisions (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-

products/applications-submissions/policies/policy-drug-medical-device-combination-products-decisions.html)

3.2.R.3 Lot Release Documentation (for Canada) (name, dosage form, manufacturer)

During the review process of NDSs and DIN-Bs, as well as SNDSs (and NCs), if necessary, based upon the change(s), test protocols and drug product consistency samples and/or material may be requested by Health Canada for testing to ensure consistency of the manufacturing process. The consistency samples should be representative of the proposed commercial process and should come from three to five consecutively manufactured lots.

The proposed test protocol format for the release package, and safety certification for any biological excipient used, if applicable (e.g. a Plasma Certificate), should be provided in this section. The documentation should include the name and title of the delegate with signing authority for lot release.

References:

Health Canada Guidance Document:

- Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs (https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/release/guidance-sponsors-program-schedule-biologic-drugs.html)

3.2.R.4 Yearly Biologic Product Report (YBPR) (for Canada) (name, dosage form, manufacturer)

Each lot of a Schedule D (biologic) drug is subject to the Lot Release Program before sale in Canada. According to the Lot Release Program, a Yearly Biologic Product Report (YBPR) is required to be submitted annually to Health Canada (BRDD) by the manufacturers of Schedule D (biologic) drugs.

The YBPR should be placed in this section.

References:

Health Canada Guidance Documents:

- Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs, (Section 5.1)
- Yearly Biologic Product Report (YBPR) Template (https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/templates/yearly-biologic-product-report-ybpr.html)

3.2.R.5 Assessment of Similarity (for Canada) (proprietary name, dosage form)

Information provided to demonstrate similarity between a biosimilar biologic drug and a reference biological drug should be provided in this section, as applicable.

References:

Health Canada Guidance Document:

- Guidance Document Information and Submission Requirements for Biosimilar Biologic Drugs (https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/information-submission-requirements-biosimilar-biologic-drugs-1.html)

3.2.R.6 On-Site Evaluation (for Canada) (name, dosage form, manufacturer)

During the review process of NDSs and DIN-Bs, as well as SNDSs (and NCs), if necessary, based upon the change(s), a pre-approval on-site evaluation (OSE) may be conducted by Health Canada to support the information provided in the application. The OSE-related documents such as the planned production schedule for all proposed manufacturing sites that cover the review period should be submitted in this section at the request of the BRDD.

3.2.R.7 Other Regional Information (for Canada) (name, dosage form, manufacturer)

Any other regional information provided to support a drug application and not captured in other sections should be provided in this section, as applicable.

3.2.R.8 Product Lifecycle Management Information (for Canada) (name, dosage form, manufacturer)

Information related to the use of the ICH Q12 regulatory tools and enablers should be provided in this section (e.g., Product Lifecycle Management Document (PLCM), Post-Approval Change Management Protocol (PACMP)). Provide a reference (hyperlink) to the PLCM in the CPID-B (Schedule D drugs) under R REGIONAL INFORMATION: *Product Lifecycle Management Information*.]

3.3 LITERATURE REFERENCES

Key literature referenced should be provided, if applicable.

End of "Module 3: Quality Guidance"

3 REFERENCE DOCUMENTS

The following lists of reference documents are intended to help identify guidance documents and templates that should be taken into consideration when preparing the quality component of a drug submission. These lists may not be all inclusive or the most current.

3.1 ICH Quality and Multidisciplinary Guidelines

Q1A Stability Testing of New Drug Substances and Products
Q1B Photostability Testing of New Drug Substances and Products
Q1C Stability Testing for New Dosage Forms
Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
Q1E Evaluation of Stability Data
Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV
Q2 Validation of Analytical Procedures: Text and Methodology
Q3C Impurities: Guidelines for Residual Solvents
Q3D Guideline for Elemental Impurities
Q5A Viral Safety Evaluation of Biotechnological/ Biological Products derived from Cell Lines of Human or Animal Origin
Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells used for Production of r-DNA Derived Protein Products
Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products
Q5D Derivation and Characterisation of Cell Substrates used for Production of Biotechnological/Biological products
Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process
Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products
Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients
Q8 Pharmaceutical Development
Q9 Quality Risk Management
Q10 Pharmaceutical Quality System
Q11 Development and Manufacture of Drug Substances (Chemical entities and Biotechnological/Biological Entities)
Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management
Q13 Continuous Manufacturing of Drug Substances and Drug Products
M4 Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use

M4Q The Common Technical Document for the Registration of Pharmaceuticals for Human Use – Quality: Quality Overall Summary (QOS) of Module 2; Module 3: Quality

M4Q The Common Technical Document-Quality Questions and Answers/ Location Issues (Q&A)

3.2 Health Canada Guidance Documents and Templates

3.2.1 General Guidance Documents

- Regulatory roadmap for biologic (Schedule D) drugs in Canada (https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/regulatory-roadmap-for-biologic-drugs.html)
- Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/clinical-trial-sponsors-applications.html)
- Guidance Document: Part C, Division 5 of the Food and Drug Regulations "Drugs for Clinical trials Involving Human Subjects"
- Organisation and Document Placement for Canadian Module 1 (available upon request).
- Clinical Trial Applications in eCTD format (available upon request).
- Preparation of Regulatory Activities in the Electronic Common Technical Document (eCTD) Format (available upon request).
- Guidance Document - Preparation of Regulatory Activities in Non-eCTD Format (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/common-technical-document/updated-guidance-document-preparation-regulatory-activities-non-ectd-electronic-only-format.html)
- Validation rules for regulatory transactions provided to Health Canada in the electronic Common Technical Document (eCTD) format

3.2.2 General Quality Guidance Documents

- Cleaning Validation Guidelines (GUI-0028)
- Good Manufacturing Practices Guide for Drug Products (GUI-0001)
- Annex 1 to the Good Manufacturing Practices Guide – Manufacture of sterile drugs (GUI-0119)
- Process Validation: Aseptic Processes for Pharmaceuticals (GUI-0006)
- Master Files (MFs) – Procedures and Administrative Requirements
- Guide to validation – Drugs and supporting activities (GUI-0029)
- Post-Notice of Compliance (NOC) Changes: Quality Document

3.2.3 Specific Biologics Quality Guidance Documents

- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines Schedule D Drugs (Biological Drugs) (GUI-0027)
- Guidance to Sponsors: Lot Release Program for Schedule D (Biologic) Drugs
- Guidance Document: Information and Submission Requirements for Biosimilar Biologic Drugs
- Guidance Document: Blood Regulations

3.2.4 Specific Biologics Quality Templates

- Certified Product Information Document – Biologics (CPID-B (Schedule D drugs))
- Quality Overall Summary – Biologics (QOS-B (Schedule D drugs))
- Yearly Biologic Product Report (YBPR) Template