Health Canada Santé Canada

GUIDANCE FOR INDUSTRY

Preparation of the Quality Information for Drug Submissions in the CTD Format: Blood Products

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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

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 scientific justification. Alternate approaches should be discussed in advance with the relevant program 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 guidance, 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 guidances.

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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. Since this guidance focuses on extending the application of the CTD format to products which are currently excluded from the ICH guidelines Q6A and Q6B, the format described within this guidance includes some product-specific considerations (e.g. relevant terminology, subheadings, illustrative examples) and modifications which are therefore, not considered to be harmonised. However, the underlying principles and application of the CTD are unchanged for all applications filed in Canada using this format. To some extent, this document supplements the relevant information from the ICH Harmonised Tripartite Guidance, *The Common Technical Document Module 2.3: Quality Overall Summary (QOS) and Module 3: Quality*, the ICH *Common Technical Document- Quality Questions and Answers/ Location Issues*, as well as the Health Canada Guidances for Industry on the preparation of various types of drug submissions in the CTD format. In addition, this document references other available domestic Quality guidances 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 Submission Management Division, Centre for Policy and Regulatory Affairs (SMD, CPRA), and the appropriate division of the Biologics and Radiopharmaceuticals Evaluation Centre (BREC), within the Biologics and Genetic Therapies Directorate (BGTD). The applicant is also advised to consult the TPD/ BGTD websites for the latest information (e.g. Notices), particularly during the transition phases of CTD implementation in Canada and as a result of the ongoing international efforts towards harmonization of CTD implementation.

1.2 Scope of this Document

Currently, this document provides guidance pertaining to human or animal blood, plasma, and serum-derived proteins or products, including immune proteins such as immunoglobulins and antibodies, coagulation proteins, and cellular blood components, and which can be purified by fractionation and other viral inactivation or removal steps, and characterized using the 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, human plasma collected by plasmapheresis, and any relevant immunizing agents. Throughout this document, this group of products are referred to as “Blood Products”.

2 LOCATION, FORMAT & CONTENT OF THE QUALITY INFORMATION

The applicant should follow the referenced ICH and domestic guidances in preparing and filing the Quality information under Module 1.4.1 (Clinical Trial Applications (CTAs) and Clinical Trial Application- Amendments (CTA-As) excluded), 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 1.4.1: Certified Product Information Document (CPID)

2.1.1 Purpose of the CPID

The *CPID* 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 SMD, CPRA and BREC retains on file for reference.

2.1.2 Selection of a CPID Template

The *CPID (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 (Schedule D drugs)* template should be used for a Biotech product, a gene therapy, a plasma-derived blood product, a natural therapeutic product, a conventional or combined vaccine.

The *CPID (Schedule C drugs)* template (or the appropriate parts of it) should be used with a drug submission in the CTD format for any radiopharmaceutical product (described under Schedule C of the Canadian *Food and Drugs Act and Regulations*), or any combination drug for human use, which has a radiopharmaceutical component.

The *Certified Product Information Document- Chemical Entities (CPID-CE (NDS))* template (or the appropriate parts of it) should be used for any product of synthetic or semi-synthetic origin (excluding Schedule D and Schedule C drugs) or any combination drug for human use, which has a synthetic or semi-synthetic component.

For a radio-labelled monoclonal antibody, a non-biological immunotoxin (e.g. a chemically-derived toxin coupled to a monoclonal antibody), or a biological immunotoxin that is not used as a vaccine (e.g. a diptheria toxin attached to a monoclonal antibody), more than one CPID template should be used. In each case, the complete or appropriate parts of the *CPID (Schedule D drugs)*, *CPID (Schedule C drugs)*, and/or *CPID-CE* templates, should be used accordingly.

The CPID (all versions) templates and their associated guidances are available on the TPD/ BGTD website(s).

2.1.3 Preparation of the CPID (Schedule D drugs)

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

In addition, the applicant is encouraged to subsequently follow the *Guidance on the CPID (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 (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 (Schedule D drugs)*. The applicant should also provide the information described under the INTRODUCTION section of the *CPID (Schedule D drugs)*.

2.1.4 Submission of the CPID

For a New Drug Submission (NDS), a Biological Drug Identification Number Application (DIN-B), or an Amendment to a DIN-B, at the request of the SMD, CPRA or BREC near the end of the review process, the applicant should submit a hardcopy of an up-to-date completed *CPID*, as part of the response to solicited information, along with one electronic copy, in Wordperfect 6/7/8/9/10.

With the filing of Supplemental New Drug Submissions (SNDSs), Notifiable Changes (NCs), Records of Changes, and Notices of Changes, as part of the drug submission review life cycle, the *CPID* may subsequently require updating, as necessary, in order to reflect information relevant to the change(s). With these types of submissions, a completed *CPID* should be provided at the time of submission filing, in hardcopy, under Module 1.4.1. In addition, one electronic copy of both the "annotated" and "clean" updated *CPID* should be provided in Wordperfect 6/7/8/9/10 under Module 1.6.

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

References:

Health Canada Guidances:

- Preparation of New Drug Submissions in the CTD Format

Health Canada Templates:

- Certified Product Information Document (*CPID (Schedule D drugs))*
- Certified Product Information Document (*CPID (Schedule C drugs)*)
- Certified Product Information Document- Chemical Entities (*CPID-CE (NDS)*)

2.1.5 Guidance on the CPID (Schedule D drugs)

Start of "Module 1.4.1 CPID (Schedule D drugs) Guidance"

INTRODUCTION

Submission File#

NDS Approval Date and Control#:

CPID 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):

Strength(s):

Route(s) of Administration:

Maximum Daily Dose:

New Active Substance (NAS)?

S DRUG SUBSTANCE (NAME, MANUFACTURER)

Manufacture (name, manufacturer)

Manufacturer(s) (name, manufacturer)

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

Description of Manufacturing Process and Process Controls (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*.]

Control of Materials (name, manufacturer)

A description of the Source and Starting Material and raw materials of biological origin used 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*.]

A summary of prepared reagents: [Insert the tabulated summary of prepared reagents from the completed Module *3.2.S.2.3*.]

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

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

Specification (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*.]

Stability (name, manufacturer)

Stability Summary and Conclusions (name, manufacturer)

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

P DRUG PRODUCT (NAME, DOSAGE FORM)

Manufacture (name, dosage form)

Manufacturer(s) (name, dosage form)

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

Batch Formula (name, dosage form)

Information on the batch formula: [Insert the tabulated summary on the batch formula from the completed Module *3.2.P.3.2*.]

Description of Manufacturing Process and Process Controls (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*.]

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

Excipients of Human or Animal Origin (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*.]

Control of Drug Product (name, dosage form)

Specification(s) (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*.]

Container Closure System (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 (name, dosage form)

Stability Summary and Conclusion (name, dosage form)

The proposed labelled storage conditions and retest date or shelf-life, including after reconstitution and in-use storage conditions (if applicable): [Insert the proposed labelled storage conditions and retest date or 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 (name, dosage form)

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

A APPENDICES

Facilities and Equipment (name, manufacturer)

Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product: [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 (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: [Insert the calculation of estimated particles/ dose, where relevant from the completed Module 3.2.A.2, under *Viral Clearance Studies*.]

End of "Module 1.4.1 CPID (Schedule D drugs) Guidance"

2.2 Module 2.3: Quality Overall Summary (QOS)

2.2.1 Purpose of the QOS

The Quality Overall Summary (QOS) is to provide Evaluators with an overview of the Quality information used to support the approval of the drug submission. During the review process, it is intended that the QOS becomes part of the Evaluator's review report.

The electronic copies of the QOS are intended to help expedite the drug submission screening and review processes, and to provide a consistent quality and format for drug submission review reports. Since the current Health Canada work environment uses Wordperfect 10.0, important documents, such as the QOS, should be submitted in Wordperfect, to provide the greatest assistance to the Evaluator(s).

2.2.2 Preparation of the QOS

The ICH Harmonised Tripartite Guidance, *The Common Technical Document Module 2: Quality Overall Summary*, the *Common Technical Document-Quality Questions and Answers/ Location Issues* document and the appropriate consolidated Health Canada *Guidance on the QOS* (provided under *2.2.4*), should be referred to for preparing the summarized Quality information required under Module 2.3. Note that several different Health Canada guidances are available on the QOS, specific by product type. These guidances are all available on the TPD/ BGTD website(s). Based upon the scope of this particular document, the guidance on the QOS under 2.2.4 is specific to Blood products and thus, distinguished as such (i.e. *QOS (Blood Products)*). For recombinant blood products, the applicant should refer to the Health Canada guidance, *Preparation of the Quality Information for Drug Submissions in the CTD Format: Biotechnological/ Biological (Biotech) Products*, instead.

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). For example, with a radio-labelled monoclonal antibody, Modules 2.3.S and 2.3.A following the *QOS (Blood Products)* guidance, and Modules 2.3.S, 2.3.P, and 2.3.A following the *QOS (Radiopharmaceuticals)* guidance, should be prepared and submitted under Module 2.3.

Within the *Guidance on the QOS (Blood Products)*, the ICH guidance on preparing the QOS has been reproduced, streamlined (i.e. it excludes the ICH guidance for NCE products), and integrated with Health Canada guidance, some clarifications, and the identification of regional information for Canada.

NOTE: A blank Health Canada Wordperfect template of the *QOS (Blood Products)* is not available. Instead, the applicant should use the exact headings and format outlined in the Health Canada *Guidance on the Supporting Quality (Blood Products) Information* (provided under *2.3.5*), If Wordperfect is not used by the sponsor (e.g. Microsoft Word is used), the *QOS (Blood Products)*, once completed, can be converted and either submitted electronically in Wordperfect or as an unlocked pdf file. The applicant should verify the content and format of any document which undergoes software conversions.

To ease the preparation of the QOS, the applicant is encouraged to follow in particular, the Health Canada *Guidance on the Supporting Quality (Blood Products) Information* (provided under *2.3.5*), on the preparation of summarized information or tabulated summaries, and which is easily identified by, "[Copy information to *QOS (Blood Products)* under a certain 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* using a similar format as in the 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 (Blood Products)* (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 (Blood Products)*, once it has been completed.

For definitions of a document within the QOS, refer to the *Common Technical Document-Quality Questions and Answers/ Location Issues* document. Since Module 2.3.R REGIONAL INFORMATION of the *QOS (Blood Products)* is not required for Canada, there are no additional document definitions provided.

Rather than duplicating information within the submission, should a cross-reference need to be made in the *QOS (Blood Products)* 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. The applicant should refer to the Health Canada draft Guidances for Industry on the preparation of various types of drug submissions in the CTD format and the ICH Guidance, *Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use- Annex* for general guidance on cross-referencing.

2.2.3 Submission of the QOS

For New Drug Submissions (NDS), the applicant is encouraged to submit a completed QOS (appropriate version) in its entirety.

For Supplemental New Drug Submissions (SNDSs) with changes to the Quality information, the applicant is encouraged 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.

For Notifiable Changes (NCs) related to the Quality information, the completion of a QOS is unnecessary.

For a Biological DIN Application (DIN-B), the applicant is encouraged to submit a completed QOS (appropriate version) for only the required subsections or parts for a DIN-B, depending upon the product, and on a case-by-case basis.

For the initial filing of a Clinical Trial Application (CTA), the applicant should submit a completed QOS (appropriate version) with, as a minimum, those subsections or parts which have a check mark (✓) beside the guidance or heading. Note that these guidances were not written specifically for CTAs and may not necessarily apply to the same extent. It is understandable that depending upon 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), where much of the quality information may be similar, the sponsor is encouraged to build upon the previously completed QOS (e.g. Phase 1 or 2 study), by making any necessary revisions or adding relevant information to update the submission and clearly identifying the changes using either coloured text or a different font. A summarized chronology of the changes which are made to the manufacturing process through drug development should be maintained throughout the clinical study phases to the NDS stage. Sponsors may complete and submit other subsections of the QOS which exclude a check mark, as that information becomes available during the course of drug development (e.g. Phase 2 and 3 CTAs), or as advance preparation of a NDS.

If a particular section contains a significant amount of information, the applicant should place it in Module 3 and cross-reference to it.

For a Clinical Trial Application-Amendment (CTA-A), regarding changes to the Quality information, the applicant is encouraged to submit an updated version of the Quality Overall Summary document with only the section(s) of the Quality Summary which have been revised or updated as a result of the change(s), and maintain the appropriate subsection numbering and the CTD format.

The applicant should consult with the SMD, CPRA or BREC for additional guidance on the technical data requirements for their particular drug submission, if necessary.

The hardcopy of the completed QOS (appropriate version) should be submitted as part of Module 2.3, including for a CTA or CTA-A (where Module 2.2 is not required and therefore, left empty). The applicant should clearly identify and separate the quality summary from the other summaries provided under Module 2, if applicable, using labelled sectional tabs (e.g. "2.3 QOS"). The applicant should refer to the Health Canada draft Guidances for Industry on the preparation of various types of drug submissions in the CTD format and the ICH Guidance, *Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use- Annex,* for further guidance on document pagination and segregation, section numbering within documents, and table of contents formatting.

Under Module 1.6 of a NDS, SNDS, or DIN-B or under Module 1.3 of a CTA or CTA-A for Canada, the applicant should submit one electronic copy of the completed QOS (appropriate version) in Wordperfect 6/7/8/9/10. The applicant should refer to the Health Canada draft Guidances for Industry on the preparation of various types of drug submissions in the CTD format for general guidance on electronic review documents.

References:

ICH Guidances:

- Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use
- The Common Technical Document-Module 2.3: Quality Overall Summary (QOS)
- The Common Technical Document-Quality Questions and Answers/ Location Issues

Health Canada Guidances:

- Guidance for Clinical Trial Sponsors- Clinical Trial Applications
- Preparation of New Drug Submissions in the CTD Format

2.2.4 Guidance on the QOS (Blood Products)

The Quality Overall Summary (QOS) 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 emphasise critical key parameters of the product and provide, for instance, justification in cases where guidances 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.

(✔) This QOS normally should not exceed 40 pages of text, excluding tables and figures. For biotech products and products manufactured using more complex processes, the document could be longer but 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 on the Supporting Quality (Blood Products) Information* (provided under *2.3.5*), 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 (Blood Products) 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 (NAME, MANUFACTURER)

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

Information from 3.2.S.2 should be included:

- (✔) Information on the manufacturer(s); [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. [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 Fractionation and/or Purification,

and Filling, storage and transportation (shipping), 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;* [Insert the process flow diagram under Fractionation and/or Purification 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*; [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.]

- 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.S.2.4* 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.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-refer to 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 (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), 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 synthesis, manufacture and/or degradation, and should summarise the basis for setting the acceptance criteria for individual and total impurities.

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 (name, manufacturer)

(✔) A brief summary of the justification of the specification(s), the analytical procedures, and validation, 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 (name, manufacturer)

(✔) Information from 3.2.S.5 (tabulated presentation, where appropriate) 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 (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 (name, manufacturer)

(✔) This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant, 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 which 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 tabulated 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 (NAME, DOSAGE FORM)

2.3.P.1 Description and Composition of the Drug Product (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 (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 which 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. [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 (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 should be provided. [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 (name, dosage form)

(✔) A brief summary on the quality of excipients, as described in 3.2.P.4, should be included. [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 (name, dosage form)

(✔) A brief summary of the justification of the specification(s), (✔) a summary of the analytical procedures, and (✔) validation, 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*.]

(✔) *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*.]

(✔) 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 (name, dosage form)

(✔) Information from 3.2.P.6 (tabulated presentation, where appropriate) 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 (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 (name, dosage form)

(✔) A summary of the studies undertaken (conditions, batches, 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 which 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 tabulated 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 (name, manufacturer)

(✔) A summary of facility information 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.] If filing a CTA/CTA-A, this summary may exclude the manufacturing flow diagrams for movement of raw materials, personnel, waste, and intermediates.

2.3.A.2 Adventitious Agents Safety Evaluation (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 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

(Not applicable for Canada.)

End of "Module 2.3 QOS (Blood Products) Guidance"

2.3 Module 3: Quality

2.3.1 Content and Extent of Supporting Quality Information

A hardcopy 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 Drugs 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 Drugs 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 Drugs 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 guidances are referenced, the relevant information described in those technical guidances 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 (*QOS* (appropriate version)) and Certified Product Information Document (*CPID (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 (Blood Products) Information* (provided under *2.3.5*), should be referred to for preparing the Quality information required under Module 3 for a Blood Products product. However, in the *Guidance on the Supporting Quality (Blood Products) Information*, the ICH guidance on preparing the quality information under Module 3 has been reproduced, streamlined by excluding the ICH guidance for NCE and Biotech products which does not apply to a blood product, 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 guidances 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 (Blood Products) Information* provides additional Health Canada guidance, clarification, where necessary, illustrative examples, and references to Health Canada Quality guidances 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 chevron symbol.

To ease the preparation of the *QOS (Blood Products)* and *CPID (Schedule D drugs)*, the applicant is encouraged to follow, in particular, the *Guidance on the Supporting Quality (Blood Products) Information* regarding the preparation of summarized information or tabulated summaries, and which is easily identified by, "[Copy information to *QOS (Blood Products)* or *CPID* under a certain section]". In addition, the applicant is encouraged to subsequently follow the *Guidance on the QOS (Blood Products)* and the *Guidance on the CPID (Schedule D drugs)* [text in square brackets], which identifies the target location in the *QOS (Blood Products)* or *CPID (Schedule D drugs)*, as the case may be, where the information from Module 3 can be conveniently "copied and pasted", once it has been completed.

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 (Blood Products) 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 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 clearly distinguish 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 radio-labelled monoclonal antibody for example, the applicable Biotech 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. (See also, the Health Canada Guidance for Industry, *Preparation of the Quality Information for Drug Submissions in the CTD Format*: *Radiopharmaceutical Products.*)

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 clearly distinguish 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");

NOTE: Under *3.2.S.2.1* and *3.2.P.3.1 Manufacturer(s)*, multiple manufacturers should be listed without the need for any unique identifiers.

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 clearly distinguish 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 clearly distinguish 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 clearly distinguish 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 clearly distinguish 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 SMD, CPRA or BREC.

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 the Health Canada draft Guidances for Industry on the preparation of various types of drug submissions in the CTD format and the ICH Guidance, *Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use- Annex*, 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**, 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, so as 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 Reference File). The approach taken should also be in accordance to the guidance on the definition of a Quality document- See the ICH Guidance, *Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use* under the *Annex: Granularity Document*. 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 a NDS, Module 3 information should be submitted in its entirety.

For a SNDS or a NC, which includes changes in the Quality information, only those subsections which 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 SMD, CPRA or BREC 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 a check mark (✓) beside the guidance or heading in Module 2.3, this information should be submitted separately in the appropriate Module 3 section.

It is understandable that depending upon 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 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 a 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 a check mark (✓) 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 Guidances:

- Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use
- The Common Technical Document- Module 3: Quality
- The Common Technical Document-Quality Questions and Answers/ Location Issues

Health Canada Guidances:

- Changes to Marketed New Drug Products Policy
- Good Manufacturing Practices
- Guidance for Clinical Trial Sponsors- Clinical Trial Applications
- Preparation of New Drug Submissions in the CTD Format

2.3.5 Guidance on the Supporting Quality (Blood Products) 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 (Blood Products) 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 (Blood Products)* 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)

The schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass should be provided, as appropriate. A brief description of the structural formula(e) of other drug(s) of similar structure, should be provided where useful. [Copy this information to the *QOS (Blood Products)* 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 (Blood Products)* under 2.3.S.1.]

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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.

References:

ICH Guidance:

- 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. [Copy this information to the *QOS (Blood Products)* under 2.3.S.2: Information on the manufacturer; Copy this information to the *CPID (Schedule D drugs)* under S DRUG SUBSTANCE: *Manufacturer(s)*]

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

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 (Blood Products)* under 2.3.S.2: Description of the manufacturing process and controls.]

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 which 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 (Blood Products)* under 2.3.S.2: Flow diagram; Copy this information to the *CPID (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 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 (Blood Products)* under 2.3.S.2: Description of the manufacturing process and controls.]

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 (Blood Products)* 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 (Blood Products)* under 2.3.S.2: Description of the manufacturing process and controls.]

References:

ICH Guidances:

- Q5A, and Q6B

Health Canada Guidances:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part I Biological Drugs
- Cleaning Validation
- Guidance on the Manufacture of Human Plasma-Derived Products Viral Safety Evaluation
- Validation Guidances for Pharmaceutical Dosage Forms

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 Guidance:

- Q6B

Health Canada Guidance:

- Acceptable Methods

For non-biological-sourced raw materials (e.g. nonmedicinal ingredients, prepared reagents) information should also be provided on the manufacturer, pharmacopoeial grade or standard, and storage (if the material is kept at non-ambient conditions). If the material is not of a pharmacopoeial grade, the specification, should be included.

Detailed information on Prepared Reagents, including their composition, specifications of the raw materials used in their preparation, a description of their preparation and sterilization, storage conditions, and shelf-life, should also be provided. In addition, a tabulated summary should be provided, for example: [Copy the completed tabulated summary to the *CPID (Schedule D drugs)* under S DRUG SUBSTANCE: *Control of Materials*: Summary of prepared reagents.]

Name of Prepared Reagent	Specifications of Raw Materials	Storage conditions	Shelf-life

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 Guidances:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part I Biological Drugs
- Product- Specific Facility Information

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.

In addition, a summary of the biological raw material(s) that are utilized as processing aids, including the source, country of origin, manufacturer, manufacturing step where used, and a brief description on the suitability for use based upon the controls evaluated (e.g. history, testing, screening), should be provided. For example, a tabulated summary could be used: [Copy the completed tabulated summary to the *QOS (Blood Products)* 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 completed tabulated summary to the *CPID (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

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 (Blood Products)* 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 DMF or SRF should be made under this section and a Letter of Authorization to allow Health Canada to review this information on behalf of the supplier should be provided under Module 1.2.6. Applicants should consult the appropriate regional guidances and/or regulatory authorities for additional guidance.

References:

Health Canada Guidances:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part 2 Human Blood and Blood Components
- Blood Collection and Blood Component Manufacturing
- Guidance on the Manufacture of Human Plasma-Derived Products Viral Safety Evaluation
- National Standards on Blood Safety

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 (Blood Products)* 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 DMF or SRF should be made under this section and a Letter of Authorization to allow Health Canada to review this information on behalf of the supplier should be provided under Module 1.2.6. Applicants should consult the appropriate regional guidances and/or regulatory authorities for additional guidance.

References:

Health Canada Guidances:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part 2 Human Blood and Blood Components
- Blood Collection and Blood Component Manufacturing
- Donor Exclusion to Address Theoretical Risk of Transmission of variant Creutzfeldt-Jakob Disease (vCJD) through the Blood Supply United Kingdom, France & Western Europe
- Guidance on the Manufacture of Human Plasma-Derived Products Viral Safety Evaluation
- National Standards on Blood Safety

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 (Blood Products)* 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 DMF or SRF should be made under this section and a Letter of Authorization to allow Health Canada to review this information on behalf of the supplier should be provided under Module 1.2.6. Applicants should consult the appropriate regional guidances and/or regulatory authorities for additional guidance.

References:

Health Canada Guidances:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part 2 Human Blood and Blood Components
- Blood Collection and Blood Component Manufacturing
- Guidance on the Manufacture of Human Plasma-Derived Products Viral Safety Evaluation
- National Standards on Blood Safety

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.

A summary of critical manufacturing steps, process controls performed, and acceptance criteria should also be provided. [Copy this summary to the *QOS (Blood Products)* under 2.3.S.2: Selection of manufacturing steps, process controls and acceptance criteria; Copy this summary to the *CPID (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 (Blood Products)* under 2.3.S.2: Discussion of selection and justification of manufacturing steps, process controls and acceptance criteria.]

Intermediates:

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 Guidance:

- Q6B

Health Canada Guidance:

- Acceptable Methods
- Guidance on the Manufacture of Human Plasma-Derived Products Viral Safety Evaluation

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 also be provided. [Copy this summary to the *QOS (Blood Products)* under 2.3.S.2: Highlight critical intermediates; Copy this summary to the *CPID (Schedule D drugs)* under S DRUG SUBSTANCE: *Controls of Critical Steps and Intermediates*: Highlight critical intermediates.]

References:

ICH Guidance:

- 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 proposed for commercial use, including data to demonstrate consistency in yield and production, and degree of purity. The validation study report 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 also be provided. [Copy this summary to the *QOS (Blood Products)* 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 and/or non-viral adventitious agents, the information from evaluation studies should be provided in 3.2.A.2.

References:

Health Canada Guidances:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part I Biological Drugs
- Cleaning Validation
- Guidance on the Manufacture of Human Plasma-Derived Products Viral Safety Evaluation
- Validation Guidances for Pharmaceutical Dosage Forms

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 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 (Blood Products)* 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 also be provided. [Copy this summary to the *QOS (Blood Products)* under 2.3.S.2: Summary of major manufacturing changes.]

References:

ICH Guidance:

- Q6B

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 and higher-order structure, post-translational forms (e.g., glycoforms), biological activity, purity, and immunochemical properties, when relevant.

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 also be provided. [Copy this summary to the *QOS (Blood Products)* under 2.3.S.3: Description of desired product; Copy this summary to the *CPID (Schedule D drugs)* under Characterisation: *Elucidation of Structure and other Characteristics*.]

References:

ICH Guidance:

- Q6B

Health Canada Guidance:

- Acceptable Methods

3.2.S.3.2 Impurities (name, manufacturer)

Information on impurities should be provided. All potential impurities, including aggregated forms, chemically-modified forms, other active components, and 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 *QOS (Blood Products)* under 2.3.S.3: Tabulated summary of data; Copy the tabulated summary to *CPID (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**			
Product Related Impurities									
TOTAL									
Process Related Impurities									
Residual Solvents									

The information should also include a discussion of results which are close to or outside limits. A rationale should be provided for the choice of tests used, the proposed limits and their qualification. A rationale for excluding any impurity test(s) from routine release testing due to trace levels, should also be provided, where applicable. [Copy this information to the *QOS (Blood Products)* under 2.3.S.3: How impurity levels are qualified.]

References:

ICH Guidances:

- Q3C, Q5C, and Q6B

Health Canada Guidances:

- Acceptable Methods

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

3.2.S.4.1 Specification (name, manufacturer)

The specification for the drug substance should be provided. For example, the specification could be presented using a table with the specification reference number, specification approval date, 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 (Blood Products)* under 2.3.S.4 Control of Drug Substance: Specification from 3.2.S.4.1; Copy this information to the *CPID (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 (Blood Products)* under 2.3.S.4 Control of Drug Substance: Drug substance standard declared; Copy this information to the *CPID (Schedule D drugs)* under Control of Drug Substance: *Specification*: Drug substance standard declared.]

References:

ICH Guidance:

- Q6B

Health Canada Guidances:

- Acceptable Methods

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

The analytical procedures used for testing the drug substance should be provided.

A summary of the analytical procedures should also be provided. (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*).) [Copy this summary to the *QOS (Blood Products)* under 2.3.S.4 Control of Drug Substance: Summary of analytical procedures.]

References:

ICH Guidance:

- Q6B

Health Canada Guidance:

- Acceptable Methods

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.

A summary of the validation of analytical procedures should also be provided. (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*).) [Copy this summary to the *QOS (Blood Products)* under 2.3.S.4 Control of Drug Substance: Summary of validation.]

References:

ICH Guidances:

- Q2A, Q2B, and Q6B

Health Canada Guidance:

- Acceptable Methods

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

Description of batches and results of batch analyses should be provided. 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 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 which 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 the a summary of this information to the *QOS (Blood Products)* under 2.3.S.4 Control of Drug Substance: 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 (Blood Products)* under 2.3.S.4 Control of Drug Substance: Tabulated summary of batch analyses.]

Test Parameter	Range of Results for in vivo study batches (Total number of batches)	Range of results for recent production batches (Total number of batches)

References:

ICH Guidances:

- Q3C, and Q6B

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

Justification for the drug substance specification should be provided.

A summary of the justification of the drug substance specification should also be provided. (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*).) [Copy this summary to the *QOS (Blood Products)* under 2.3.S.4 Control of Drug Substance: Summary of justification of the specification(s).]

References:

ICH Guidances:

- Q3C, and Q6B

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 should be provided. [Copy this information to the *QOS (Blood Products)* under 2.3.S.5.]

References:

ICH Guidance:

- Q6B

Health Canada Guidance:

- Acceptable Methods

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 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 (Blood Products)* under 2.3.S.6.]

Non-compendial methods (with validation) 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:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part I Biological Drugs

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 retest date or shelf-life, as appropriate. 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, retest date or shelf-life, where relevant. [Copy this summarized information to the *QOS (Blood Products)* under 2.3.S.7: Summary of the studies; Copy this summarized information to the *CPID (Schedule D drugs)* under S DRUG SUBSTANCE: Stability: *Stability Summary and Conclusions*.]

References:

ICH Guidances:

- Q1A(R2), Q1B, Q5C and Q6B

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

The post-approval stability protocol and stability commitment should be provided.[Copy this information to the *QOS (Blood Products)* under 2.3.S.7: Post-approval stability protocol.]

References:

ICH Guidances:

- Q1A(R2), and Q5C

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 than 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 (Blood Products)* under 2.3.S.7: Tabulated summary]

References:

ICH Guidances:

- Q1A(R2), Q1B, Q1E, Q1F, Q2A, Q2B, Q5C, and Q6B

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 (Blood Products)* 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 Guidance:

- 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. 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 (Blood Products)* under 2.3.P.2: discussion of information.]

[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.

References:

ICH Guidance:

- Q6B

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.

➤ 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. [Copy this information to the *QOS (Blood Products)* under 2.3.P.2: confirmation]

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 formulation (i.e. composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g., dissolution) 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 affected, should also be provided. For example: [Copy the completed tabulated summary to the *QOS (Blood Products)* 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:

Health Canada Guidance:

- Acceptable Methods

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 process described in *3.2.P.3.3* that can influence the performance of the product should be discussed.

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:

Health Canada Guidance:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part I Biological Drugs

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.

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. [Copy this information to the *QOS (Blood Products)* under 2.3.P.3: Information on the manufacturer; Copy this information to the *CPID (Schedule D drugs)* under P DRUG PRODUCT: *Manufacturer(s)*.]

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). A tabulated summary of this information may be provided. For example: [Copy the completed tabulated summary to the *QOS (Blood Products)* under 2.3.P.3: Information on batch formula; Copy the completed tabulated summary to the *CPID (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)		

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 (Blood Products)* under 2.3.P.3: Flow diagram; Copy this information to the *CPID (Schedule D drugs)* under P DRUG PRODUCT: *Description of Manufacturing Process and Process Controls.]*

A narrative description of the manufacturing process, including packaging, that 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 (Blood Products)* 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 (Blood Products)* 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 (Blood Products)* under 2.3.P.3: Description of manufacturing process and 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 Guidance:

- Q6B

Health Canada Guidance:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part I Biological Drugs
- Guidance on the Manufacture of Human Plasma-Derived Products Viral Safety Evaluation

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) 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* and *3.2.P.4.3 Validation of the Analytical Procedures* for Control of Excipients and/or *3.2.P.5.2 Analytical Procedures* and *3.2.P.5.3 Validation of the Analytical Procedures* for Control of the Drug Product information.

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

References:

ICH Guidance:

- Q2A, Q2B, and Q6B

Health Canada Guidance:

- Acceptable Methods

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 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 also be provided. [Copy this information to the *QOS (Blood Products)* under 2.3.P.3: Description of process validation.]

References:

ICH Guidance:

- Q6B

Health Canada Guidances:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part I Biological Drugs
- Cleaning Validation
- Guidance on the Manufacture of Human Plasma-Derived Products Viral Safety Evaluation
- Process Validation: Aseptic Processes for Pharmaceuticals
- Validation Guidances 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 (Blood Products)* 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 DMF, or SRF should be made under this section and a Letter of Authorization to allow Health Canada to review this information on behalf of the supplier should be provided under Module 1.2.6. Applicants should consult the appropriate regional guidances and/or regulatory authorities for additional guidance.

References:

ICH Guidance:

- Q6B

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 Guidances:

- Q2A and Q6B

Health Canada Guidance:

- Acceptable Methods

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 Guidances:

- Q2A, Q2B, and Q6B

Health Canada Guidance:

- Acceptable Methods

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 (Blood Products)* under 2.3.P.4: Control of Excipients]

References:

ICH Guidances:

- 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: [Copy the completed tabulated summary to the *QOS (Blood Products)* under 2.3.P.4: Control of Excipients; Copy the completed tabulated summary to the *CPID (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 a DMF, or SRF should be made under this section and a Letter of Authorization to allow Health Canada to review this information on behalf of the supplier should be provided under Module 1.2.6. Applicants should consult the appropriate regional guidances and/or regulatory authorities for additional guidance.

References:

ICH Guidances:

- Q5A, and Q6B

Health Canada Guidances:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part I Biological Drugs
- Guidance on the Manufacture of Human Plasma-Derived Products Viral Safety Evaluation
- Product Master Files
- Site Reference File

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 a DMF, or SRF should be made under this section and a Letter of Authorization to allow Health Canada to review this information on behalf of the supplier should be provided under Module 1.2.6. Applicants should consult the appropriate regional guidances 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 (Blood Products)* under 2.3.P.4: Control of Excipients]

References:

Health Canada Guidances:

- Product Master Files
- Site Reference File

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 specification reference number, specification approval date, test parameter(s), method type, method code, source, and acceptance limit(s) at release, shelf-life or for both. For a blood product which has not been subjected to any validated or effective viral inactivation or removal steps during manufacturing, it may be appropriate for the release specification(s) of the drug product to include an acceptable and validated test for any relevant bloodborne transmissible disease marker(s) of concern. [Copy this information to the *QOS (Blood Products)* under 2.3.P.5: Specification(s) from *3.2.P.5.1*; Copy this information to the *CPID (Schedule D drugs)* under Control of Drug Product: *Specification(s)*: specification(s) for the drug product.]

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

References:

ICH Guidance:

- Q6B

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

The analytical procedures used for testing the drug product should be provided in detail.

A summary of the analytical procedures should also be provided. (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*).) [Copy this summary to the *QOS (Blood Products)* under 2.3.P.5: Summary of analytical procedures.]

References:

ICH Guidances:

- Q2A and Q6B

Health Canada Guidance:

- Acceptable Methods

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.

A summary of the validation of analytical procedures should also be provided. (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*).) [Copy this summary to the *QOS (Blood Products)* under 2.3.P.5: Summary of validation.]

References:

ICH Guidances:

- Q2A, Q2B and Q6B

Health Canada Guidance:

- Acceptable Methods

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

A description of batches and results of batch analyses should be provided. 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 which 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 (Blood Products)* 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 (Blood Products)* under 2.3.P.5: Tabulated summary of batch analyses.]

Test Parameter	Range of Results for in vivo study batches (Total number of batches)	Range of results for recent production batches (Total number of batches)

References:

ICH Guidances:

- 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, 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 which are close to or outside limits. A rationale should be provided for the choice of tests used, the proposed limits and their qualification. 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 (either provided under *3.2.P.5.5* or *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 (Blood Products)* under 2.3.P.5: Characterisation of impurities.]

References:

ICH Guidances:

- Q5C, and Q6B

Health Canada Guidance:

- Acceptable Methods

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

Justification for the proposed drug product specification(s) should be provided.

A summary of the justification of the drug product specification 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 characterisation of impurities (*3.2.P.5.5*).) [Copy this summary to the *QOS (Blood Products)* under 2.3.P.5: Summary of justification of specification(s).]

References:

ICH Guidance:

- 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 should be provided, if not previously provided in "3.2.S.5 Reference Standards or Materials". [Copy this information to the *QOS (Blood Products)* under 2.3.P.6.]

References:

ICH Guidance:

- Q6B

Health Canada Guidance:

- Acceptable Methods

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

A description of the container closure systems 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 and identification (and critical dimensions, with drawings where appropriate). [Copy this information to the *QOS (Blood Products)* under 2.3.P.7; Copy this information to the *CPID (Schedule D drugs)* under P DRUG PRODUCT: Container Closure System.]

Non-compendial methods (with validation) 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:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part I Biological Drugs

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, retest date or shelf-life, where relevant. [Copy this summarized information to the *QOS (Blood Products)* under 2.3.P.8: Summary of studies undertaken; Copy this summarized information to the *CPID (Schedule D drugs)* under P DRUG PRODUCT: Stability: *Stability Summary and Conclusion*.]

References:

ICH Guidances:

- Q1A(R2), 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 stability commitment should be provided. [Copy this information to the *QOS (Blood Products)* under 2.3.P.8: Post-approval stability protocol; Copy this information to the *CPID (Schedule D drugs)* under P DRUG PRODUCT: Stability: *Post-Approval Stability Protocol and Stability Commitment*.]

References:

ICH Guidances:

- Q1A(R2), and Q5C

Health Canada Guidance:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part I Biological Drugs

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. 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 (Blood Products)* under 2.3.P.8: Tabulated summary.]

Information on characterisation of impurities is located in *3.2.P.5.5*.

References:

ICH Guidances:

- Q1A(R2), Q1B, Q1E, Q1F, Q2A, Q2B, Q5C and Q6B

Health Canada Guidance:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part I Biological Drugs

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. 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 manufactured or manipulated in the same areas as the applicant's product should be included. [Copy this information to the *CPID (Schedule D drugs)* under A APPENDICES: Facilities and Equipment.]

A summary description of 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.

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 in this section, should also be provided. [Copy this summary to the *QOS (Blood Products)* under 2.3.A.1.]

References:

Health Canada Guidances:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part I Biological Drugs
- Cleaning Validation
- Process Validation: Aseptic Processes for Pharmaceuticals
- Product-Specific Facility Information
- Site Reference File

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:

The detailed information regarding the routine manufacturing control of adventitious agents, such as bacteria, mycoplasma, and fungi, typically using well-established (e.g., pharmacopoeial) analytical procedures, 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.

With respect to other non-viral adventitious agents, such as transmissible spongiform encephalopathy agents and prions, the detailed information, should be placed in 3.2.A.2.

Detailed information should be provided on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents, and prions). 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.

A summary of the measures used to avoid and control non-viral adventitious agents during production, should also be provided. [Copy this summary to the *QOS (Blood Products)* under 2.3.A.2: Discussion on measures.]

References:

ICH Guidances:

- Q5A, 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 are considered safe, and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable. The applicant should refer to Q5A, and Q6B for further guidance.

A summary of the measures used to test, evaluate, and eliminate the potential risks of viral adventitious agents during production, should also be provided. [Copy this summary to the *QOS (Blood Products)* under 2.3.A.2: Discussion on measures.]

References:

Health Canada Guidance:

- Guidance on the Manufacture of Human Plasma-Derived Products Viral Safety Evaluation

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*). Information on the donor suitability, blood or plasma unit testing and screening for appropriate bloodborne 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. This may also include a tabulated summary 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*. For example: [Copy this summary to the *QOS (Blood Products)* under 2.3.A.2: Discussion on measures.]

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

References:

ICH Guidances:

- Q5A

Health Canada Guidances:

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part I Biological Drugs
- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part 2 Human Blood and Blood Components
- Blood Collection and Blood Component Manufacturing
- Guidance on the Manufacture of Human Plasma-Derived Products Viral Safety Evaluation
- National Standards on Blood Safety

Testing at appropriate stages of production

The selection of virological tests that are conducted during manufacturing (e.g., testing on bulk or final product, 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, and 3.2.P.5.1*).

A brief summary of the virological test(s) conducted during manufacturing (e.g., on bulk or final product as post viral clearance testing), at which critical step(s) and intermediate(s), and the conclusion of the testing results, should also be provided. [Copy this summary to the *QOS (Blood Products)* under 2.3.A.2: Discussion on measures.]

References:

Health Canada Guidance:

- Guidance on the Manufacture of Human Plasma-Derived Products Viral Safety Evaluation

Viral Testing of Intermediates

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 also be provided. [Copy this summary to the *QOS (Blood Products)* under 2.3.A.2: Discussion on measures.]

References:

ICH Guidances:

- Q5A, and Q6B

Viral Clearance Studies

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 (Blood Products)* 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*).

A tabulated summary of the reduction factors for viral clearance, should also be provided. For example: [Copy the completed tabulated summary to the *QOS (Blood Products)* under 2.3.A.2: Tabulated summary of reduction factors; Copy the completed tabulated summary to the *CPID (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, where relevant, should also be provided. [Copy this information to the *QOS (Blood Products)* under 2.3.A.2: Calculation of estimated particles/dose; Copy this information to the *CPID (Schedule D drugs)* under A APPENDICES: Adventitious Agents Safety Evaluation: calculation of estimated particles/dose.]

References:

ICH Guidance:

- Q5A

Health Canada Guidance:

- Guidance on the Manufacture of Human Plasma-Derived Products Viral Safety Evaluation

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) noncompendial 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. [Copy the summary of the excipients described under 3.2.A.3, their suitability for use, and a discussion on their potential risk(s) to the *QOS (Blood Products)* 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 guidances 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 for the 3-5 consecutively manufactured or consistency drug product lots from each production site or facility, should be provided. (During the review process, executed batch records for drug substance may be requested, if necessary.)

Blank batch records should be submitted only when they are different from executed batch records. In this case, a summary of the discrepancies, and the rationale for the differences, should also be submitted.

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 Bureau of Medical Devices in Canada, should be provided.

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

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

3.3 LITERATURE REFERENCES

Key literature referenced should be provided, if applicable.

End of "Module 3: Quality (Blood Products) Guidance"

2.4 Other Information

Further to support the approval of drug submissions, pursuant to section C.08.004 of the *Food and Drugs Regulations*, under Sections C.08.002(3) of the *Food and Drugs Regulations*, the applicant should submit test protocols and drug product consistency samples and/or material to the BREC for testing and evaluation during the review process for NDSs and DIN-Bs, as well as for SNDSs and NCs, if necessary, based upon the change(s).

For CTAs, and CTA-As (if applicable) specifically for vaccines, clinical test samples should also be submitted for testing and evaluation during the review process. For other CTAs and CTA-As, clinical test samples may need to be submitted upon request of the SMD, CPRA or BREC; although generally, the applicant is expected to separately submit a completed FAX-BACK form for the clinical trial lot near the end of the review process or after a No Objection Letter is received and before any clinical lot can be used.

Where additional information is necessary, such as the number of sample vials required for testing, the applicant should consult with the SMD, CPRA or BREC.

During the review process of NDSs and DIN-Bs, as well as SNDSs (and NCs), if necessary, based upon the change(s), other information related to the pre-approval on-site evaluation (e.g. production schedule), should be submitted at the request of the SMD, CPRA or BREC.

References:

Health Canada Guidances:

- Review/Testing/Approval of Biological Drug Lots
- Inspection of Biologics Manufacturers
- Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers/Labellers, Distributors and Importers

3 REFERENCE DOCUMENTS

The following lists of reference documents are intended to help identify guidances 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. Sponsors should consult the TPD/BGTD website(s) for the latest versions of the documents listed below:

3.1 ICH Quality and Multidisciplinary Guidances

Q1A(R2)	Stability Testing of New Drug Substances and Products
Q1B	Photostability Testing of New Drug Substances and Products
Q1C	Stability Testing for New Dosage Forms
Q1E	Evaluation of Stability Data
Q1F	Stability Data Package for Registration Applications in Climatic Zones III and IV
Q2A	Text on Validation of Analytical Procedures
Q2B	Validation of Analytical Procedures: Methodology
Q3C	Impurities: Residual Solvents.
Q5A	Viral Safety Evaluation of Biotechnological/ Biological Products derived from Cell Lines of Human or Animal Origin
Q5C	Quality of Biotechnological Products: Stability Testing of Biotechnological/ Biological Products
Q6B	Specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological Products
M4O	Organisation of the Common Technical Document for the Registration of Pharmaceuticals for Human Use (Step 5, updated September 2002; Annex revised November 2003 and updated January 2004)
M4Q	The Common Technical Document- Module 2.3: Quality Overall Summary (QOS); Module 3: Quality (Step 5, updated September 2002)
M4Q Q&A	The Common Technical Document-Quality Questions and Answers/ Location Issues (Step 5, July 2003)

3.2 Health Canada Guidances and Templates

3.2.1 General Guidances

- Changes to Marketed New Drug Products Policy (04/94)
- Guidance for Clinical Trial Sponsors- Clinical Trial Applications (2003)
- Preparation of New Drug Submissions in the CTD Format (DRAFT, 2003)

3.2.2 General Quality Guidances

- Acceptable Methods (07/94)
- Cleaning Validation Guidances (05/00)
- Good Manufacturing Practices (1998)
- Process Validation: Aseptic Processes for Pharmaceuticals (09/96)
- Product Master Files (04/94)
- Site Reference File Guideline (07/00)
- Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers/Labellers, Distributors and Importers (DRAFT, 11/00)
- Validation Guidances for Pharmaceutical Dosage Forms (05/00)

3.2.3 Specific Biologics Quality Guidances

- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part I Biological Drugs (06/99)
- Annex to the GMP Guidances, Good Manufacturing Practices Guidances (GMPs) for Schedule D Drugs, Part 2 Human Blood and Blood Components (12/99)
- Blood Collection and Blood Component Manufacturing (1992)
- Donor Exclusion to Address Theoretical Risk of Transmission of variant Creutzfeldt-Jakob Disease (vCJD) through the Blood Supply United Kingdom, France & Western Europe (08/01)
- Guidance on the Manufacture of Human Plasma-Derived Products Viral Safety Evaluation (04/01)
- Guidance to Industry: Changes to Product-Specific Facility Information (03/99)
- Guidance to Industry: Product-Specific Facility Information (03/99)
- Inspection of Biologics Manufacturers (04/92)
- National Standards on Blood Safety (07/00)
- Review/Testing/Approval of Biological Drug Lots (10/96)

3.2.4 Specific Biologics Quality Templates

- Certified Product Information Document (*CPID (Schedule D drugs)*) (05/04)