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Updated Guidance Documents for Industry

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

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Background

- Originally developed in 2004 to reflect our expectations with respect to the quality requirements for **Module 2 and 3**.
  - With the intent to decrease the number of clarification requests due to missing information

- Four CTD Guidance documents were developed:
  - **Biotechnological/biological (Biotech) Products:** Produced from recombinant or non-recombinant cell-culture expression systems or isolated from tissue and body fluids, and which can be highly purified and characterized (e.g. monoclonal antibodies, hormones, enzymes, cytokines)
  - **Conventional Biotherapeutic Products:** Isolated from biological sources such as tissues, organs and body fluids (e.g. pancreatic enzymes, anterior pituitary extracts, snake venom, and allergenic substances)
  - **Blood products:** include any human or animal blood, plasma, and serum-derived proteins or products, including immune proteins such as immunoglobulins, antibodies, coagulation proteins, which can be purified by fractionation and other viral inactivation or removal steps, and characterized using an appropriate array of analytical procedures
  - **Vaccines:** All vaccines to be authorized for human use

What's new in 2021 and 2024? - Final document release in April 2024

- The three CTD Guidance documents applicable to ***Conventional Biotherapeutic Products***, ***Biotechnological/biological (Biotech) Products*** and ***Blood Products*** **were merged** into one document
  - Were sharing more than 90% of the content
  - Decrease the number of guidance documents on the website
- **Modernized** the document with replacement of outdated information (e.g., organizational structure, guidance documents) and with clarifications on what need to be provided under each CTD section to reflect our current expectations.
- The guidance **remains compliant** with the text in ICH M4Q entitled ***"The Common Technical Document for the Registration of Pharmaceuticals for Human Use (2002)"***
- A **QOS-B template** has been developed
- The **CPID-B template** has been updated to be in line with the revised Guidance for Industry and to incorporate the principles of ICH Q12.

Scope

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

- These guidelines also apply to protein products used for ***in vivo*** **diagnosis** (e.g. monoclonal antibody products used for imaging).

- The following products are **out of scope** and excluded from this document:
  - Vaccines for human use
  - Gene and cell therapy products
  - Cellular blood components
  - Human plasma collected by plasmapheresis, and any relevant immunizing agents
  - Radiopharmaceuticals (Schedule C drugs)

Module 2 – Quality Overall Summary (QOS)

- A **QOS-B blank template** will be made available to the sponsor to avoid the filing of the QOS-CE with biological applications. The QOS-CE is not suitable for biological applications.

- The use of the Canadian QOS-B template **will not be mandatory**. Companies will be authorized to continue using global QOS template. However, the use of the Canadian QOS will reduce the number of clarification requests for missing information.

- The requirement to submit an annotated QOS in support of a post-approval change has been replaced with the requirement to submit an updated version of the QOS**, with only the section(s) which have been revised or updated respective of the change(s).**

- Clarification was made that an **IMPD** may be submitted in lieu of a **QOS** for CTAs and CTA-As to reflect the current practice.

Module 2 – QOS (cont'd)

- Clarification was made that ***Process validation*** and ***Method validation*** is not required for CTAs and CTA-As.

- Clarification was made that information on the Container Closure System used in the stability studies is required in the ***Stability section***.

- ***Facility information*** is no longer required for CTAs.

- ***Appendices:*** For approved products, a summary of **facility information** and **cleaning procedure/validation** has been added as new information to be provided in the QOS

- ***Regional information:*** A summary of the **biosimilarity assessment** provided in Module 3 under 3.2.R.5 should be provided in the QOS. Currently, this is not a requirement.

Extracts from the QOS-B template

- **Some subsections has been added:**

2.3.S.2.3.3 Cell bank system

2.3.3.1 Cell Bank lineage
2.3.3.2 MCB characterization
2.3.3.3 WCB characterization
2.3.3.4 End-of-production cell banks
2.3.3.5 Post-production cell bank
2.3.3.6 Genetic stability

2.3.S.2.4 Control of Critical Steps and Intermediates (common name, manufacturer)

2.3.S.2.4.1 Identification and control of critical steps

2.3.S.2.4.2 In-process data

2.3.S.2.4.3 Justification of acceptance criteria for in-process controls

2.3.S.2.4.4 Intermediates

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

2.3.S.2.5.1 Stage 1 – Process design

2.3.S.2.5.2 Stage 2 – Process qualification/validation

2.3.S.2.5.3 Stage 3 – Continued/ongoing process verification

Extracts from the QOS-B template (cont'd)

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

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

2.3.S.3.1.1 Introduction

2.3.S.3.1.2 Primary structure

2.3.S.3.1.3 Secondary structure

2.3.S.3.1.4 Higher-order structure

2.3.S.3.1.5 Molecular weight

2.3.S.3.1.6 Molecular size, aggregation and fragmentation

2.3.S.3.1.7 Charge isoforms

2.3.S.3.1.8 Post-translational modifications

2.3.S.3.1.9 Biological activity

2.3.S.3.1.10 Structure function relationship

Module 3: Quality – Drug Substance

- **S.2.1 Manufacturer(s)**: Clarification has been added regarding what should be provided in the Manufacturer table (e.g. for testing sites).

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

***If more than one testing site, the test(s) performed at each site should be listed.

Module 3: Quality – Drug Substance (cont'd)

S.2.3 Control of Materials:

- Detailed information on Prepared Reagents is proposed to be **deleted** as it is not part of ICH M4Q.

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

- The emphasis is on the Control of Source and Starting Materials of **Biological Origin**

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

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

Module 3: Quality – Drug Substance (cont'd)

S.2.3 Control of Materials (cont'd):

- Clarification has been added regarding the need to file **Qualification Protocols** used to generate **Master Cell Bank (MCB)** and **Working Cell Bank (WCB)**.
  - Once pre-approved, this allow the filing of new WCB as Level III change instead of Notifiable Changes

S.2.5 Process Evaluation and/or Evaluation Studies:

- Re emphasis that information provided in the validation report should support the current manufacturing process and the **scale** proposed for commercial use (added "scale").
- Confirmed that the **process** validation study report **and the protocols** for the extent of reuse and regeneration of columns and membranes should be provided, including in-process test results and data from relevant manufacturing batches, to demonstrate consistency in the quality and safety of the drug substance during production.

Module 3: Quality – Drug Substance (cont'd)

- **S.3.2 Impurities:** Summary tables have been proposed for reporting **process-related** and **product-related** impurities.

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

The information should also include a discussion of results that are close to or outside limits. A rationale should be provided for the choice of tests used, the proposed limits and their qualification, ***including a control strategy for each impurity. Proposed limits should be supported by evidence such as toxicological limits, NOAEL, PDE etc.***

NOAEL: No-observed-adverse-effect-level
PDE: Permitted daily exposure

Module 3: Quality – Drug Substance (cont'd)

S.4.3 Validation of Analytical Procedures:

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

- For analytical methods used at release or stability that have been transferred during development, information demonstrating **technical transfer qualification** for the **non-pharmacopoeial assays** should be provided **(DELETED)**.

S.4.4 Batch Analysis:

- Clarification that the Certificates of Analysis no longer need to be provided.

Module 3: Quality – Drug Substance (cont'd)

S.4.5 Justification of Specification:

- Clarification that although the drug substance specifications are only one part of the total control strategy, this section is appropriate to summarize the **overall drug substance control strategy**.

S.5 Reference Standards or Materials:

- Clarification has been made that a **detailed summary** of **Qualification Protocols** used for the qualification of future Reference Standards should be submitted.
  - Once pre-approved, this allow the filing of new Reference Standards as Level III change instead of Notifiable Changes

Module 3: Quality – Drug Substance (cont'd)

S.7 Stability:

- Clarification that the information on the **stability batches** and **batch lineage** should also be provided. This information may be reported using a proposed summary table.

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

Module 3: Quality – Drug Product

P.2 Pharmaceutical Development:

P.2.2.1 - Formulation Development:

- Clarified that a tabulated summary of the composition of the formulations used in clinical trials **and the batches numbers associated with the formulations** should also be provided

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

Module 3: Quality – Drug Product (cont'd)

P.2 Pharmaceutical Development:

P.2.3 – Manufacturing Process Development:

- Clarification that differences between the manufacturing process(es) used to produce **pivotal clinical batches** and the **commercial process** described in *3.2.P.3.3* that can influence the performance of the product should be discussed. ***The use of flow diagram(s) comparing the different manufacturing process(es) is also recommended.***

P.2.6 – Compatibility

- Added that: Compatibility studies should be conducted for the drug product using **closed system transfer devices** (e.g., with intravenous administration sets) and should include **extractable** and **leachable** studies with the dosage devices. Compatibility study design including dose preparation and administration components, type of materials, stress conditions, hold times, temperatures, stability indicating tests and results should also be provided.

Module 3: Quality – Drug Product (cont'd)

- **P.3.1 Manufacturer(s)**: Clarification has been added regarding what should be provided in the Manufacturer table (e.g. for testing sites, importers and distributors).

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

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

Module 3: Quality – Drug Product (cont'd)

- **P.3.2 - Batch formula:** Clarification that the anticipated range of commercial batch size should be based on the available manufacturing experience.
  - For a **product under development**, the proposed range should not exceed **± 20% of the current manufacturing experience** with the drug product, **unless supported by pharmaceutical development data**.

- **P.5.3 - Validation of analytical procedures:** Clarification that for analytical methods used at release or stability that have been transferred during development, information demonstrating **technical transfer qualification** for the **non-pharmacopoeial assays** should be provided **(DELETED)**.

- **P.5.4 - Batch analysis:** Clarification that in the description of the batch analysis, this description should include the batch number, production scale, date of manufacture, production site, manufacturing process and use. Confirmation should be provided that the batch analysis data results reported in the submission were generated by the company responsible for routine testing of the drug product.
  - Clarification that the Certificates of Analysis no longer need to be provided.

Module 3: Quality – Drug Product (cont'd)

- **P.5.5 - Characterization of impurities:** Clarification that the impurity limits (including degradation products arising from manufacturing, storage, or detected in stability study batches) should be set taking into account **the totality of what will be administered to the patient** (i.e. in combination with other drugs, diluent or IV infusion solution).

- **P.5.6 - Justification of Specifications (Same as for Drug Substance)**: Clarification that although the drug product specification is only one part of the total control strategy, this section is appropriate to summarize the **overall drug product control strategy**.

- **P.6 - Reference Standards or Materials:** Clarification that a **detailed summary** of **Qualification Protocols** used for the qualification of future Reference Standards should be submitted.
  - Once pre-approved, this allow the filing of new Reference Standards as Level III change instead of Notifiable Changes
  - At the time of filing of a marketing application (NDS or DIN-B), it is recommended that a **two-tiered reference standard program** be in place.

Module 3: Quality – Drug Product (cont'd)

- **P.7 - Container Closure System :** Clarification that information on the neck opening size for vials should be provided as part of the Container Closure System information.

- **P.8: Stability:** Clarification that information on the stability batches and batch lineage should also be provided. This information may be reported using a proposed summary table.

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

Module 3: Quality – Appendices

A.1 - Facilities:

- A diagram should be provided illustrating the manufacturing flow, including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas as well as the **room classification**.
- Clarification that a summary of the **environmental monitoring program**, including data from the **last 12 months in classified areas**, should be provided.

A.2 - Adventitious Agents Safety:

- Clarification that viral reduction studies should be performed using both new and used resins, unless it can be justified that data for new resins are appropriate to leverage for aged resins.
- Clarification that the detailed **safety factor calculation** should be performed based on a **worst-case scenario.**

Module 3: Quality – Regional Information

- **R.1 - Executed Batch Records:**
- Clarification that Executed Batch Records **are no longer required** at time of filing to support a marketing application (NDS or DIN-B) or any post-NOC changes (S/NDS, NC or DIN-B). However, these may be requested during review and should be available within 15 days upon request.

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

- In cases where Executed Batch Records are requested, the most current Master Batch Records should be submitted ***only when they are different from executed batch records***.

Module 3: Quality – Regional Information

- **R.2 - Medical devices**:
- Clarification has been provided on the classification of **combination products** with a medical device.
  - For those combination products classified as **drugs**, relevant product information should be provided as per this guidance document. Compliance with the international standards (e.g., ISO 13485 requirements) should be demonstrated, when applicable.
  - Where the device forms part of the primary packaging (i.e. is in contact with the product during storage), it should be described under P.7.

Module 3: Quality – Regional Information (cont'd)

- **R.4:** New section added for "**Yearly Biologic Product Report**".

- **R.5:** New section added for **"Assessment of Similarity"**.
  - Information provided to demonstrate similarity between a biosimilar biologic drug and a reference biological drug should be provided in this section, as applicable.

- **R.6:** New section added for **"On Site Evaluation".**
  - The OSE-related documents such as the planned production schedule for all proposed manufacturing sites that cover the review period should be submitted in this section at the request of the ORA, CBE or CERB.

- **R.7:** New section added for **"Other Regional Information".**
  - Any other regional information provided to support a drug application and not captured in other sections should be provided in this section, as applicable.

- **R.8:** New section added for **"Product Lifecycle Management Information"**.
  - Information related to the use of the ICH Q12 regulatory tools and enablers should be provided in this section (e.g., Product Lifecycle Management Document (PLCM), Post-Approval Change Management Protocol (PACMP)).

Revisions to the CPID-B

- CPID-B has been revised to incorporate the principles of ICH Q12
- A completed annotated and clean copy of the CPID-B should be provided at the time of submission filling for an NDS
- Proposed revisions:
  - Additional information on batch scale should be provided under ***Description of Manufacturing Process and Process Controls***
  - Additional information on MCB and WCB used in the manufacture of the drug substance should be provided in ***Control of Materials***
  - A section of the Reference Standards or Materials has been added under the drug substance and drug product section
  - A section on the Container Closure System has been added under the drug substance section
  - Additional information regarding the anticipated range of commercial batch size should be provided under ***Drug Product, Batch Formula***
  - A summary of all facilities and equipment information is to be provided under ***Appendices – Facilities and Equipment***
  - Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant should be included and has been expanded to include information on the *host cells or cell line*

Modernisation of ICH M4Q(R1) (ongoing)

- M4Q(R1) format does not follow typical pharmaceutical development and manufacturing processes and presents a segmented view of product development and manufacturing rather than an holistic one;
- M4Q(R1) format fragments the presentation of critical product information across multiple sections which introduces redundancy, lengthens regulatory submissions and review, and reduces overall efficiency;
- Information is not provided in a way that facilitates effective understanding of lifecycle management across a product line or facility;
- There are no designated locations for concepts, such as established conditions and overall control strategy, that have been developed or given greater focus since the elaboration of ICH M4Q(R1);
- There is no discussion about how to manage emerging concepts, such as advanced manufacturing, data management and analytics, analytical development (as per Q14);
- There are no clearly designated locations for multicomponent complex products, such as antibody-drug conjugates, combination products (pharmaceutical/device), or tissue engineered products.

Thank you!